SHOCK AND CIRCULATORY HOMEOSTASIS

Transactions of the Third Conference

September 14, 15 and 16, 1953, Princeton, N. J.

Edited by

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WHEN I WAS on a destroyer out at Bikini in 1946 I was fascinated listening to our radio operator as he tested communication equipment He would ask another ship through his radio, "How do you hear me?" and the answer often would come back, "I hear you Nine-Nine-Nine" That meant that everything was satisfactory Of the three nines, one was for intensity, one for clarity, and one for meaning

The Josiah Macy, Jr Foundation has organized and devoted a large portion of its resources to the support of its Conference Program because the officers are cognizant of the fact that there is considerable obstruction to communication and mutual understanding across the disciplines and specialties, and that this, in fact, is one of the major factors delaying scientific advance We feel that there are psychological as well as semantic factors contributing to the difficulty of communication, people, even in arguments with one another, are too much inclined to make statements *at* rather than to communicate *with*, others. I think that we are inclined to forget, though, that the real question is, are these words and statements those which are likely to convey to the listener the whole or even a small part of what I would like to express

I have a feeling that we should be very much concerned with the other fellow's receiving set and not with our own transmitter alone If the other person doesn't seem to understand us, it may not be enough merely to increase the power of our transmission, we must try to find the obstruction in his receiving set and to see what kind of filters and resistors he uses So, if we call out to the interprofessional No-Man's-Land, "How do you hear me?" and the reply comes back, "I hear you Nine-Nine-Nine," we have the beginning of communication What we try to do in these conferences conducted by the Foundation is to set the stage for meaningful communication

With the accelerating rate at which new knowledge is accumulating and with the increasing recognition that nature is of one piece, it becomes evident that the continued isolation of the several branches of science from one another is a serious obstacle to scientific progress Nowhere in science is the need for "combined opera-

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tions" more evident than in medicine Today, to be effective, medical research and practice must embrace data from all the disciplines including nuclear physics at one end of the spectrum and cultural anthropology at the other, for advances in one field are frequently dependent upon knowledge derived from quite another discipline.

Although the fertility of the multidiscipline approach is thus recognized, universities, and scientific societies and journals, which are usually restricted to one small area of a field in their coverage, have not yet made adequate provision for channels of interdisciplinary communication We do not wish to compete with the formal scientific meetings or with the scientific journals which have established patterns and formats for the presentation of material Our purpose at the meetings is to keep an informal atmosphere and to encourage the exchange of methods, research plans, concepts and difficulties, which cannot be done if there is formal speech making

The Foundation has endeavored to meet the need for interdisciplinary communication by bringing together for a series of two-and-a-half day annual conferences a small group of investigators, representing in so far as possible all the branches of science related to a chosen problem Participants in these informal conferences over a five-year period develop a feeling of friendship, trust and mutual respect which in turn promotes communication, cross-fertilization of ideas and cooperation The success of such an endeavor, however, is dependent upon full participation of all members in the discussion Accordingly attendance at any conference is limited to twenty-five

Under the guidance of Dr Willard C Rappleye, President of the Foundation since 1942, the Conference Program has been gradually expanded and enlarged until during 1953 it included twelve different groups which met annually to discuss a wide variety of problems in the field of medicine and the closely related disciplines Our plan is to discontinue the meetings of each group at the end of five years

In order to share with a wider group of investigators and students the essential quality of these conferences and to give others an insight into the functions of the scientific mind, the informal nature and tempo of the discussions, as far as possible, are preserved in the published transactions

FRANK FREMONT-SMITH, M D.,
Medical Director

EXPERIENCES WITH SHOCK IN THE KOREAN THEATER

JOHN M HOWARD, *Captain*, (MC), USA
Department of Surgery
Baylor University College of Medicine

THE SURGICAL RESEARCH TEAM of the Medical Corps of the United States Army has worked in Korea during the past two years I have had the privilege during that time of observing the response to injury and therapy of approximately 4,500 battle casualties, and of studying in detail the response of several hundred of the more severely injured These observations were made a few miles behind the front lines in a Mobile Army Surgical Hospital

We found that every organ, every system which we have been able to study, and presumably every cell in the body, takes part in the response to trauma This response of the entire body is not limited to a few minutes or hours, it may continue for days or even weeks Its duration and magnitude are roughly proportional to the degree of injury It involves the autonomic nervous system, adrenal cortex, cardiovascular system, liver, kidneys, pancreas, gallbladder, gastrointestinal tract, bone marrow, skeletal muscle, lymphatic system, the metabolism of carbohydrates and proteins and the wound and its effects on the clotting mechanism

I should like to present certain of our observations on the cardiovascular response to injury, with the hope that they may stimulate discussion as to the meaning of the problems we encountered. The survival of the battle casualty depends, to a very great extent, on the competence of his circulation This is at the heart of the problems associated with resuscitation

Five syndromes emerge from our observations Using blood pressure as the primary criterion, they are compensation, overcompensation, decompensation, hypertension associated with renal failure, and secondary hypotension after anesthesia and operation

COMPENSATION

A loss of from 10 to 25 per cent of the blood volume can be tolerated without a drop of pressure.* With an injury of this degree,

**The Physiological Effects of Wounds* Board for the Study of the Severely Wounded U S Government Printing Office, Washington, D C, 1951

the immediate compensation is through the response of the casualty's autonomic-cardiovascular system. Time and again we saw the pressure drop precipitously when any additional trauma was added We saw two casualties die from a passive movement to the x-ray facilities, they went from a condition of compensated shock into severe shock Such patients are extremely sensitive to the anesthetic agents, pentothal, nitrous oxide, and ether, particularly to pentothal, which cause them to decompensate The responsibility of the surgeon, of course, is to recognize the state of compensation and correct the blood volume deficit before the compensatory mechanism is blocked by the use of anesthesia

OVERCOMPENSATION-HYPERTENSION

Overcompensation occurs as a hypertensive response to injury There is a tremendous burst of sympathetic activity overlying a relatively intact circulatory mechanism Hypertension may develop a few minutes after injury, or be delayed in onset for one or two hours Thirty soldiers were selected for study who were hypertensive on admission to the forward hospital at an average time of 3.5 hours after wounding, with a spread of from one to eighteen hours These casualties, without previous hypertension, had a systolic pressure between 140-240 mm Hg

Heymans Exactly what do you mean by "overcompensation"? In what system does overcompensation occur?

Howard I am using blood pressure as my criterion

Heymans Are you saying, Dr Howard, that it is overcompensation in the sense of a reaction to low blood pressure, and that in some conditions an organism, instead of going back to normal levels of blood pressure, shifts the pressure to a high level, and so overcompensates? I do not assume that such a condition really exists If the blood pressure reaches too high a level, I think another factor must have come into the picture

Howard What I am trying to do is develop the thesis that the responses of man to all magnitudes of injury, are similar, and that moderate and severe injuries produce the same response but different clinical pictures, because, in some cases, the injury is out of proportion to the patient's ability to compensate

Shorr Do you mean, Dr Heymans, that instead of this being an extension of the same process, it may involve another process?

Heymans Yes

Shorr You see, Dr Howard, you are using "overcompensation" as a continuation of the same process Dr Heymans means that it may not necessarily be the same, and that another process may

have come into play which is responsible for the hypertension

Howard Possibly the same mechanism is there, but another etiological stimulus has been added

Dawes I just wish to be sure about those patients who, after injury, had a high pressure Did they have a normal pressure under ordinary circumstances beforehand, or did they have high blood pressure when you first examined them?

Howard These men, by physical examination, previously had normal pressure, and subsequently during their hospital stay had normal pressure

Folkow Is it not possible that this "overcompensation" or hypertensive response, is induced by the probable massive stimulation of pain fibers? Excitation of such fibers will in most cases increase the sympathetic discharge rate, with an increased blood pressure as a consequence

Howard Yes, but I should like to emphasize the fact that putting them to sleep does not drop the blood pressure

Fremont-Smith The principle of overcompensation is well established

Heymans Not for blood pressure homeostasis

Fremont-Smith Hyperemia?

Heymans That is an abnormal situation, but we cannot call it physiological compensation

Howard Is hyperemia, the local response to trauma, any more "abnormal" than the systemic response to trauma?

Fremont-Smith Perhaps our problem is words

Heymans I think when we use the word "compensation" with regard to a drop in arterial blood pressure, it means that there has been a physiological compensation in an effort to bring the blood pressure back to the normal level, but I do not think we can consider that the same mechanism is involved when the blood pressure goes too high I should prefer to use different terms and speak of compensation as a physiological mechanism However, when the blood pressure gets too high, I am quite sure that another mechanism, or another factor, is involved, because normally it would not do that It may be a question of terms However, the meaning of these terms must be clear, because otherwise we shall get into difficulty in interpretation

Shorr An overcompensation, to your mind, would be such excessive vasoconstriction as actually to impair profoundly the blood flow through the tissues

Heymans Yes If you take ten per cent of the blood volume out

of a dog, he compensates and brings his pressure to normal It never would go to a higher level if nothing else were introduced which would push it to a higher level

Dawes If you bleed an animal, the blood pressure will always fall, the compensation mechanism then begins to function Therefore, you would say that anything which raises the pressure above normal would be overcompensation or some other factor However, you are looking at this entirely from the standpoint of hemorrhage

Heymans No, I am also thinking of the condition of shock

Knisely When we make an analytical study of the observation that one category of patients responds by a measurable drop in pressure, and another by an increase in pressure, we find we have to use two different languages the one physiological, and the other clinical I should like to add that the blood agglutinates in response to the crushing of parts of the body Dr Howard, why do you define injury in terms of hémorrhage alone?

Howard We by no means believe that hemorrhage is the only injury But it is the one that can be measured and most readily treated

Knisely Following the hemorrhage, there is a decreased flow

Nickerson I think it is extremely important to make a distinction here The first step in gaining useful information from these observations is to analyze the mechanisms If the carotid sinus is responsible for compensation, and the so-called "overcompensation" is due to afferent impulses arising from other areas, that is the first and perhaps the most fruitful distinction we can make, and one that will lead us, not only to a more complete interpretation of what is going on, but also to more rational methods for combatting it I hope we can obtain information regarding the origin of the impulses that are responsible for the activity or hyperactivity of the vasoconstrictors

Burton We have come to think in terms of cybernetics We had thought about the control mechanisms before, but did not have this long word for it In control mechanisms in physics, one has the phenomenon of "hunting," which one might call "overcompensation," and it is quite difficult to correct it But I think the systems of homeostasis in the living organism are so well "designed" that we do not usually encounter hunting in the body, in fact, I do not know many cases of it Thus, I think this is a rather fundamental point which Dr Heymans has raised

Folkow As regards Dr Howard's statement that the hypertensive response remains even during sleep, it should be stressed that

stimulation of pain fibers in animals raises blood pressure both in narcotized and decerebrated preparations, showing that this reflex response, involving pain fibers and sympathetic vasomotor fibers, is operating at a medullary level does not need the actual perception of the pain for its establishment

Acheson It seems to me that Dr Howard has three categories, and that in labeling them he has been anticipating what he will tell us later The words "normotensive," "hypertensive," and "hypotensive" will describe his first three cases I do not understand how these effects could be explained from what he said, and I am confident that he is going to give us some evidence on the subject

Howard In the example I gave you, the clinical picture was quite characteristic Each of the 30 men had extremity wounds of a noncritical nature, and only four had associated visceral wounds None of them died of their wounds, or required massive transfusion to support them Although blood volume determinations were done in only a few, the maximal deficit appeared to be about 25 per cent The skin was clinically normal in color and temperature The pulse pressure and mean pressure were elevated Therefore, there appeared to be an increase in cardiac output, and probably a selective vasoconstriction

Two-thirds of the patients had fractures of relatively small bones the tibia, or bones of the foot In cases of amputation, it was a minor one, not of the thigh or midcalf, but of the ankle Two-thirds of the wounds were caused by small firearms, fired at close range, or mines.

Most of the patients were in severe pain, which is unusual for the injured soldier, occasionally they were quite restless The usual pulse range was from 80-100, but occasionally a bradycardia of 64-66 was noted Occasionally a tachycardia was present The patients were insensitive to analgesics in terms of their effect on blood pressure They were quite sensitive to pentothal, and to autonomic blockade with other drugs The question is were afferent impulses from the extremities, or products of tissue breakdown, the cause of the response?

Because of the precipitous drop in pressure with anesthesia, it was postponed for 6 hours in one instance, and 3 5 hours in another In neither case did the response lessen Analgesics were then tried Many of the patients had already received morphine before admission Two were given demerol, and two morphine intravenously in an amount sufficient to put them to sleep, but the hypertension persisted

of a dog, he compensates and brings his pressure to normal It never would go to a higher level if nothing else were introduced which would push it to a higher level

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Fine The criterion was the normotensive state?

Howard: Yes, although it was not reached.

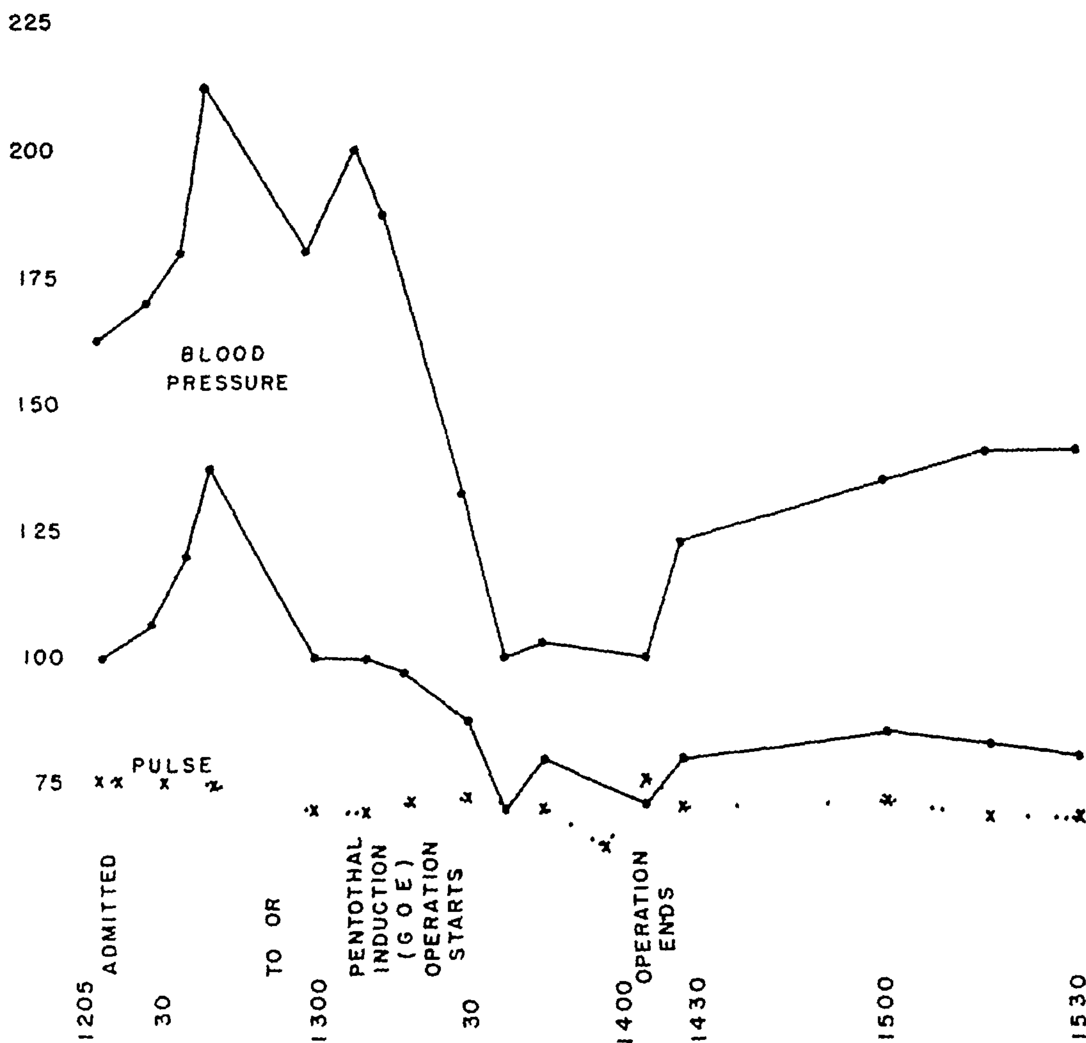


FIGURE 1 Patient S D S, age 39 years Hypertensive response to injury, traumatic amputation of foot

Figure 1 shows that with a pulse pressure of 100 mm, and a pulse rate of approximately 75, the induction with pentothal was followed by a drop in systolic pressure of 100 mm, and that the pressure did not return postoperatively to the hypertensive level The latter was a characteristic finding If we then accept the action of the pentothal as being that of a sympathetic depressant .

Heymans I am sorry, but as a pharmacologist I cannot agree that pentothal injected intravenously is a real ganglionic blocking agent

In an effort to define the mechanism, two patients were given 5 mg of regitine intravenously, a drug recommended for use in diagnosing pheochromocytomas This dose would block, and possibly reverse, the pressor response to epinephrine, but would have little effect on the pressor responses to norepinephrine or sympathetic nerve stimuli In one instance there was a sharp drop in pressure, and in another a modest drop

Hexamethonium, in a dose of 25 mg., was given intravenously to three of the casualties This drug is reported to block conduction across the sympathetic ganglia In all three instances, the pressure dropped precipitously

Dr. Robert Dunning Dripps called attention to the frequent fall in blood pressure which the battle casualty experienced after pentothal, and stated that he believed it to be a sympathetic blocking agent Whatever the etiology, the mechanism of the hypertensive response appears clinically to be an increased cardiac output, and possibly a selective vasoconstriction, through the mechanism of the sympathetic nervous system

Nickerson. What is the evidence for this being predominantly an increase in cardiac output?

Howard I was using the marked increase in pulse pressure as an index of increased stroke volume output

Nickerson One reason I asked was that, at least in the case of regitine, one would expect a blockade of the responses of the blood vessels to stimuli from epinephrine, but not of the heart

Howard Even if there were an increase in the circulating epinephrine?

Nickerson That is right

Liljestrand May I ask whether the inhalation of oxygen had any effect on the blood pressure in these patients?

Howard I cannot answer that

Dawes Were they blue?

Howard No None of these patients with wounds showed clinical evidence of anoxia

Liljestrand There might be anoxia present, particularly in the carotid body, which might be one explanation of the high blood pressure It would be interesting to observe the effect of oxygen

Burch Did you measure the venous pressure?

Howard No

Fine How did you decide that it was advisable to wait for six hours before administering the anesthesia?

Howard We didn't We waited up to six hours for the pressure to return to normal

Fine The criterion was the normotensive state?

Howard Yes, although it was not reached

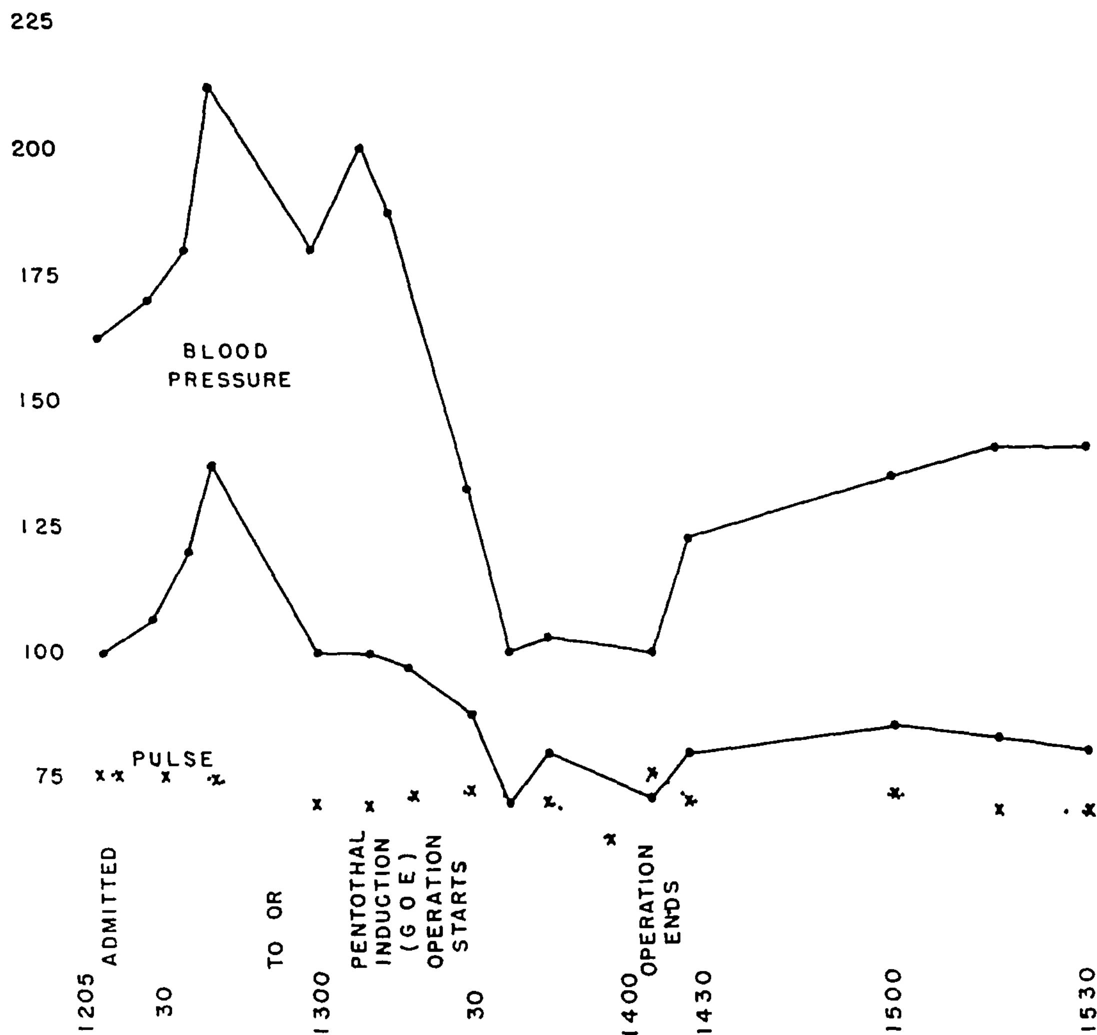


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Comroe Dr Dripps and his group (1) have found that patients deeply anesthetized with pentothal do not seem able to constrict their peripheral vessels in response to raised airway pressure, whereas patients under cyclopropane anesthesia retain this ability Of course, that is not proof that transmission through sympathetic ganglia is depressed or blocked. The only direct work that I am familiar with is that of Dr Martin Larrabee (2) at Johns Hopkins, who has found that barbiturates depress ganglionic transmission

Nickerson: If I recall correctly, they began to get effects at what you might call the maximum anesthetic dose At the same level of anesthesia, thiopental produced less depression of ganglionic transmission than did ether or chloroform

Dawes When the operation ends and the patient is normotensive, has he any pain?

Howard. Yes

Burton. There is a very good rule which applies to pulse pressure, namely, that the pulse pressure, times the heart rate, times the distensibility of the aorta, is an index of the cardiac output However, if the distensibility of the aorta has changed, as we can very well imagine would occur under the sympathetic discharge, then an increase in pulse pressure does not connote an increase in cardiac output, does it? I think that unless one had measurements of cardiac output, it would be very difficult to prove

Richardson I think such doses of pentothal as were given to this series of patients would be expected to have an effect on the central nervous system, but not on the peripheral autonomics

Heymans In most animal experiments, small amounts of pentothal, or other barbiturates, do not interfere with ganglionic transmission, but doses of pentothal sufficient to induce anesthesia exert a very marked depression on the vasomotor centers This can be shown in experiments, and rules out the physiological mechanisms of blood pressure homeostasis That, I believe, is why the blood pressure of the patients Dr Howard mentioned was brought down

Richardson Would you also agree that a drop to a similar level might occur in a perfectly normal individual? It would probably be not as much, because the pressure is not so high

Heymans I am not sure, because it is possible that in an injured patient, the normotensive level of pressure is also knocked out by hemorrhage, trauma, or so on

Shorr You think that the normal homeostatic mechanisms are not operating in that case?

Richardson They are just depressed

Heymans. Of course, we do not know However, according to experimental observations, if we take from 10 to 20 per cent of the blood volume from a dog, or induce any marked trauma, the normal homeostatic mechanisms of blood pressure are markedly depressed. It is quite possible that in the patient having been subjected to trauma or some bleeding, the normal homeostatic mechanisms are exhausted because they have been used up to compensate for the drop in blood pressure, and that pentothal is just increasing that tendency. The total drop in blood pressure cannot be compensated for That is my explanation

Stead In a normal person from whom you take blood, one of three reactions occurs the blood pressure remains the same, goes up, or falls In the early stages of blood loss, the pressure is dependent on the activity of the autonomic system If enough blood is removed, the pressure will of course always fall, but in the earlier stages the arterial pressure is determined by factors other than the amount of blood loss My guess would be that these patients would behave in the same way to the general stimuli, regardless of whether they had lost blood or not

Dr Hickam (3) studied normal students taking final medical examinations, and showed that the rises in blood pressure might be due to an increase in peripheral resistance, to a rise in cardiac output, or a combination thereof.

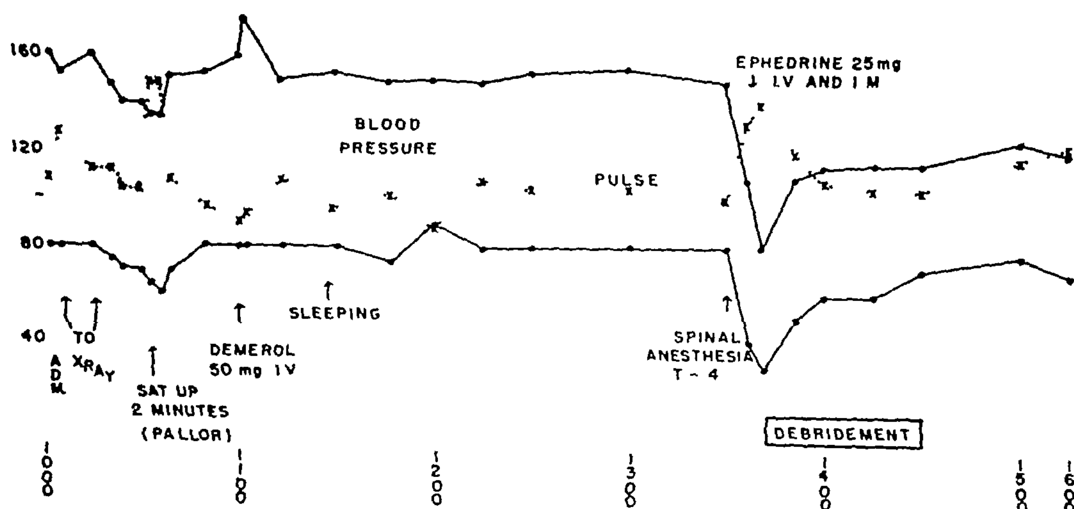


FIGURE 2 Patient P M, 19 years old Hypertensive response to injury, fractures of feet and legs

Howard Figure 2 gives the reactions of a patient with a blood pressure of roughly 160/80 In 3 5 hours, it stabilized under demerol It then fell under spinal anesthesia and responded to ephedrine

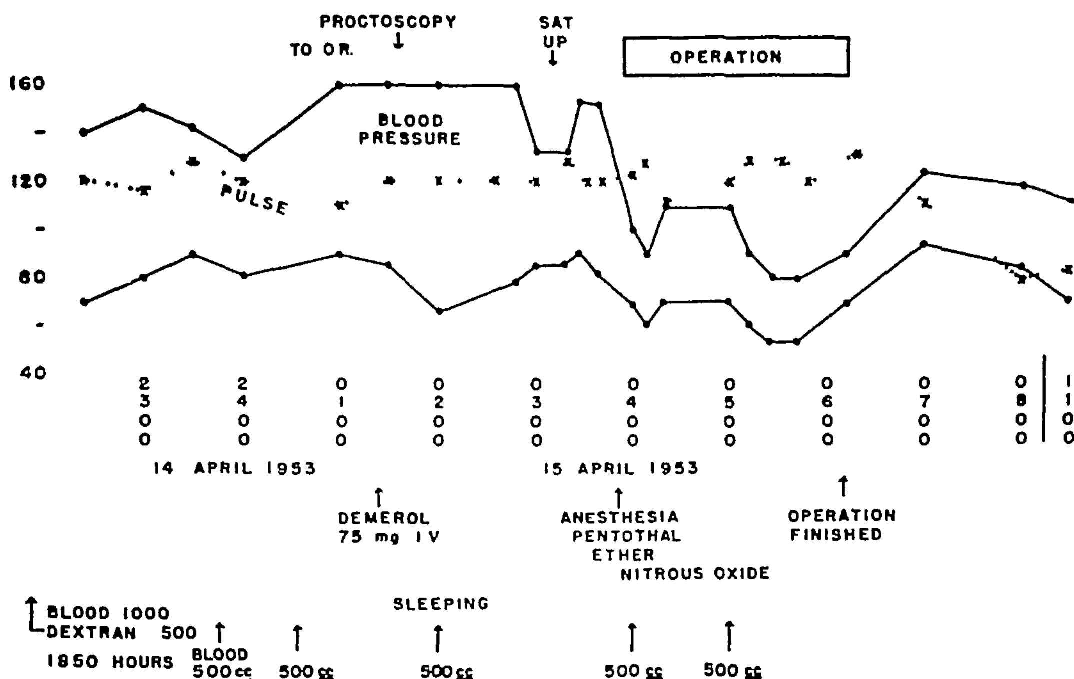


FIGURE 3 Patient J T S, age 23 years Hypertensive response to injury

Figure 3 shows the persistence of the response for five hours There was a moderate hypotension associated with changes in posture, then a sharp drop with pentothal anesthesia Postoperatively the pressure did not rise again

Acheson I have observed patients who were induced with pentothal, and the continuation of anesthesia was accomplished with nitrous oxide I should like to know whether you had patients whom you did not induce with pentothal, and whether you think it was the general anesthesia, rather than the induction with pentothal, which was involved

Howard Patients who had spinal anesthesia were not induced with pentothal Pentothal was not used for anesthesia, it was used for induction I am certain there were exceptions to the last statement

Lawton I should like to ask how long the blood pressure may be sustained if no anesthetic is given

Howard The longest period of time the patients were observed was up to six hours after admission

Lawton It would appear that this would not be "hunting" if it were sustained for six hours at a rather constant level

Heymans If pentothal is given to a normal dog, just to induce anesthesia, his blood pressure generally does not fall However, this dose of pentothal may knock out his normal compensatory mechanisms for homeostasis of blood pressure If hypertension has been induced by cutting the buffer nerves, the same amount of pentothal will provoke a drop in blood pressure. I am not surprised that a dose of pentothal which would not induce a drop

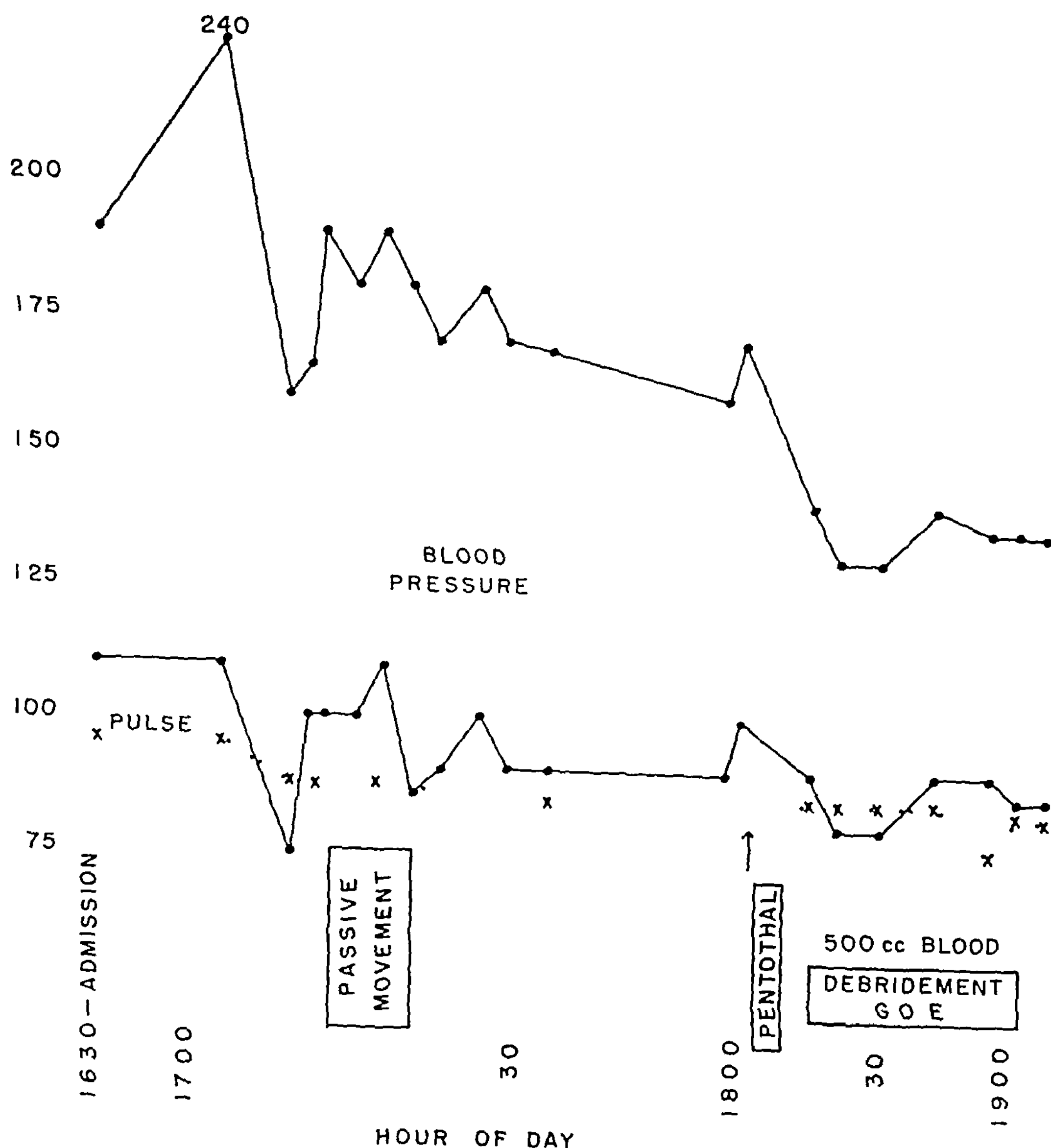


FIGURE 4 Patient R R, 21 years of age Hypertensive response to injury, fractured femur

Howard Figure 2 gives the reactions of a patient with a blood pressure of roughly 160/80 In 3 5 hours, it stabilized under demerol It then fell under spinal anesthesia and responded to ephedrine

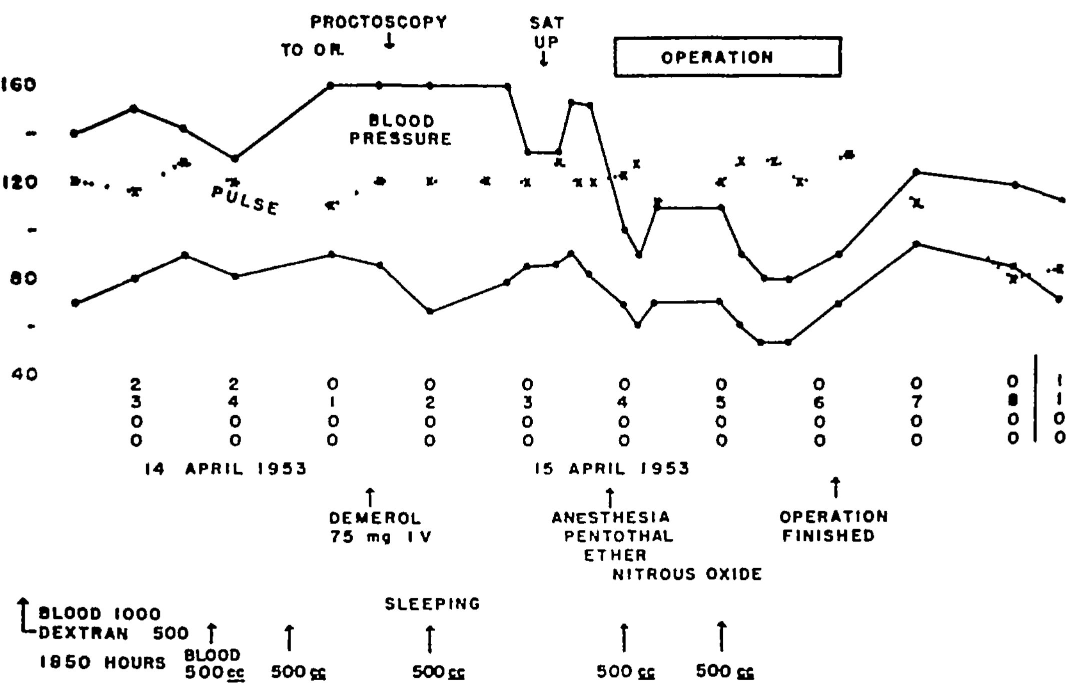


FIGURE 3 Patient J T S, age 23 years Hypertensive response to injury

Figure 3 shows the persistence of the response for five hours There was a moderate hypotension associated with changes in posture, then a sharp drop with pentothal anesthesia Postoperatively the pressure did not rise again

Acheson I have observed patients who were induced with pentothal, and the continuation of anesthesia was accomplished with nitrous oxide I should like to know whether you had patients whom you did not induce with pentothal, and whether you think it was the general anesthesia, rather than the induction with pentothal, which was involved

Howard Patients who had spinal anesthesia were not induced with pentothal Pentothal was not used for anesthesia, it was used for induction I am certain there were exceptions to the last statement

Lawton I should like to ask how long the blood pressure may be sustained if no anesthetic is given

Howard The longest period of time the patients were observed was up to six hours after admission

Lawton: It would appear that this would not be "hunting" if it were sustained for six hours at a rather constant level

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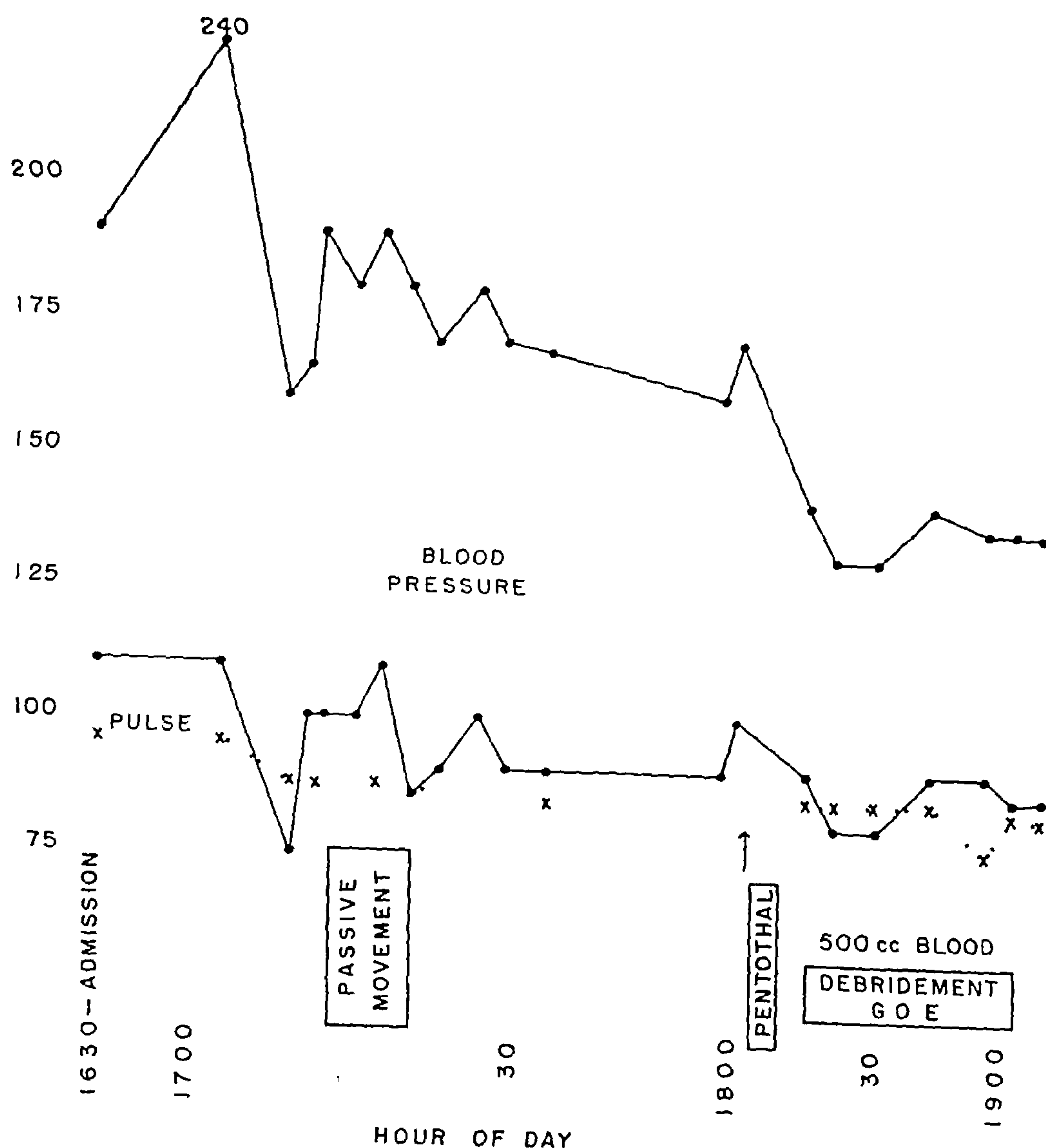


FIGURE 4 Patient R R, 21 years of age Hypertensive response to injury, fractured femur

in blood pressure in a normal person, would cause a drop in a patient whose high blood pressure was due to injury The extent of the drop would depend on the amount of pentothal injected of course

Burton· I understand Dr Heyman's point, but I should like to know whether the response of blood pressure to ephedrine is normal

Richardson It would be normal if it were given intravenously

Acheson How do you know that the curve in Figure 2 is a response to ephedrine?

Richardson You do not

Burton If we inject something and the curve goes up, we say it is a physiological response

Acheson However, it was given when the curve was very low

Howard Figure 4 shows another casualty Here the pressure remained hypertensive, but labile, during passive movement Again there was a drop following pentothal

Burch Do you have any data concerning the adrenal function in these patients?

Howard. In these particular patients, no, but we were never able to demonstrate adrenal cortical insufficiency in any casualty

FIGURE 5 Patient J C, age 24 years Fracture of patella Hypertensive response to injury.

Figure 5 shows that with the patient sleeping much of the time, hypertension persisted for approximately six hours With the patient asleep hexamethonium, in a dose of 25 mg given intravenously, produced a sharp drop in pressure from approximately 200 to 86 systolic, and from 90 to 0 diastolic

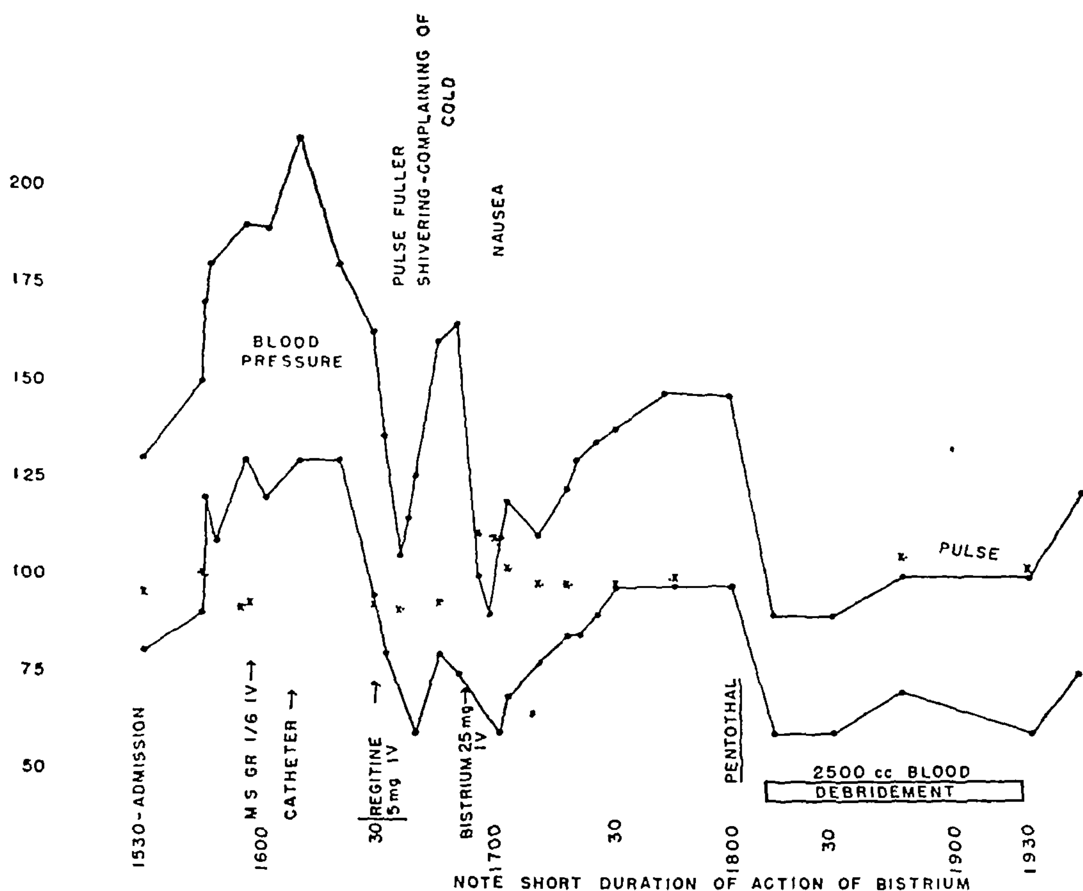


FIGURE 6 Patient E F, 24 years of age Hypertensive response to injury, fracture of humerus

Figure 6 shows the reactions when three drugs were given* When regitine was administered, the pressure dropped precipitously, but then rose rapidly However, it did not rise to the previous level When hexamethonium (bistrium) was given intravenously, a sharp drop occurred, after which there was a gradual rise With pentothal, the same response occurred This leads to the conclusion that whatever the etiology of this hypertension, it would seem to be mediated through the sympathetic nervous system, and that its blockade dropped the pressure to normal or hypotensive levels

*In collaboration with Dr A C Corcoran

Green If you wanted to produce a sympathetic blocking effect, I should think you would have to give at least 0 5 mg per kilogram of regitine

Nickerson In that particular patient, I think you would have to say that the effect of regitine was due to the fact that there was a large amount of circulating epinephrine or norepinephrine, 5 mg is not a sympatholytic dose of regitine I do not think you could compare the effect with that of hexamethonium

FIGURE 7 Patient H D , age 20 years Hypertensive response to injury

Howard Figure 7 shows a patient with a modest drop in systolic pressure, and a marked drop in diastolic pressure He was quite insensitive to pentothal, and a large amount was required to keep him on the operating table Postoperatively there was a continuation of his hypertension for a day or so, and then it disappeared When the patient was brought back to the operating room four or five days later, he again became hypertensive, and required a large dose of pentothal, and other anesthetic agents

Could it be that in the patients who were sensitive to hexamethonium and pentothal, the response was mediated primarily through the nerves themselves, probably from afferent stimulation

of the extremities, whereas the component of the patient with restlessness, evidence of fear, and insensitivity to drugs, was largely that of the circulating epinephrine with psychological factors as its etiology?

Nickerson Did this patient receive regitine?

Howard No

DECOMPENSATION—HYPOTENSION

Howard I should like to make some generalizations on the observations of the patients who were decompensated. Table I is a summary of the reaction to injury of 30 patients who were admitted with a blood pressure which was imperceptible It demonstrates the following three points first, an obvious one, that hemorrhage is more difficult to control from the abdomen than from the extremities, second, the amount of blood required for resuscitation is a better index of prognosis than is the blood pressure on admission, third, the abdominal injuries carry a higher mortality

Fremont-Smith What was the criterion used in determining how much blood they should get?

Howard Restoration of blood pressure

Burch How much blood loss did you replace? Was it pint for pint?

Howard We frequently felt we were replacing much more than pint for pint We could never prove that by blood volume measurement

Burch Why couldn't you establish a ratio?

Howard We spent a year in trying to find out why we were using so much blood Was there loss of blood, destruction of blood or pooling of blood? I am not certain We could not demonstrate a high blood volume Yet we used as much as 42 pints of blood, and much of it postoperatively

Burch Did you study the urobilinogen excretion in the stools?

Howard These patients could not give a specimen for five or six days However, there was a sharp peak in urine urobilinogen after injury *

Stead Was there any difference in the autopsy findings in these people who received the 42 pints of blood?

Howard There was not a uniform finding

Burch Do you have any idea where the blood went?

Howard We would occasionally find blood pooled in the skeletal muscle, or pulmonary edema However, after extensive study we could not say that the blood was present in the vascular tree

*Unpublished data from the Surgical Research Team in Korea

TABLE I

Resuscitation of Battle Casualties—Blood Pressure Imperceptible on Admission

	Total Sample		Receiving 15 or More Pints of Blood			Receiving Less Than 15 Pints of Blood		
Injury	Number	Mortality	Number	No Died	Mortality	Number	No Died	Mortality
Abdominal Only	10	70%	7	7	100%	3	0	0
Abdominal and Extremity	6	50%	6	3	50%	0	—	—
Extremity Only	14	7%	8	1	12.5%	6	0	0
Total	30	37%	21	11	52%	9	0	0

Richardson Dr Howard, do you think there is any chance that in some of your patients you may have administered too much blood, and hence hurt rather than helped them?

Howard Occasionally that was a possibility, but I am much more certain that it saved lives

Selkurt Did you find hemorrhage into the intestine?

Howard No

Fine You would have no way of determining how much blood or plasma was lost into the area of the wound, would you?

Howard No The extremity wounds, of course, characteristically result in hemodilution

Burton What about the size of the liver in these people who had so much blood loss?

Howard It was not markedly changed

Fine You do not list the time of the death of these people Was there an immediate mortality during the transfusions, or did death occur some time thereafter?

Howard It was an early mortality We lost very few patients after the first 24 or 36 hours, unless we lost them from renal failure Once the patients got by the first 48 hours and the threat of renal failure, the mortality must have been a fraction of one per cent

Alexander: Did you get any cases of venous thrombus and pulmonary embolus?

Howard In our entire experience we had two patients with pulmonary embolus, both of whom had injury to the peripheral vascular system

Fine Some of these deaths seem to have had nothing to do with a deficiency in blood volume

Howard I think, Dr Fine, that they were definitely related to the original injury and the shock that resulted

Fine This is at variance with what Simeone reported on cases in World War II they found that the wounded men who were in shock because of blood loss could always be resuscitated by giving blood as late as 14 hours after wounding

Howard We could always restore the blood pressure, but we might not always be able to maintain it during anesthesia and postoperatively Without exception, we were able to raise the pressure before anesthesia if hemorrhage could be controlled, and if no wound to the central nervous system were present

Fine But you could not always restore the blood volume deficit

Burch How can the blood volume deficit be measured if one cannot account for 42 pints of injected blood? For example, how

can one pint less than normal be detected? It was probably not measured accurately, at any rate, the blood pressure data failed to reveal adequately the hemodynamic state

Howard. You are certainly right

Alexander In reference to the fate of the transfused blood, it has been our experience in the experimental laboratory, that if one approaches these problems with classical pathological methods one does not get very far For obvious reasons, pathological techniques are designed to recognize chronic changes in tissues I wonder whether the autopsy examinations have been approached by other than routine pathology It would require someone with the conviction that the blood was to be found, and with the desire to meet the challenge of finding it by criteria other than those used in the usual postmortem examination

Howard Lt Joseph Strawitz, of the Surgical Research Team, Army Medical Corps, has devoted much of his time to finding it In Korea, he looked for it grossly by weight measurements We have been trying to develop measurements for chemical analysis, but have not completed them as yet

Knisely Were the disintegration products of red blood cells looked for carefully in the Kupffer cells of the liver and the macrophages of the spleen?

Howard Yes, and we also studied, simultaneously, the pigment metabolism We were using bank blood, from ten days to three weeks of age, and as you will recall, one uniformly obtains a modest rise in the plasma hemoglobin, which rapidly disappears Although I am sure that by staining, one would be able to find the breakdown products, one would not be able to quantitate them

Knisely That is agreed, but if one does find a breakdown product in the phagocytes, then at least one knows it was caused by something

Fine When hemorrhage had stopped we usually found, by blood volume measurements, that infused plasma or blood could be almost entirely accounted for within the circulation But in septic peritonitis or tourniquet shock, when the blood volume deficit was severe, plasma or blood transfusions, as judged by blood volume determinations, did not succeed in correcting the deficit

The deficits, as measured before and after giving these fluids are, we believe, valid determinations What happens to infused fluid in a normal person is not altogether mysterious Everything except red cells leaves the circulation, with differing velocities for water, electrolyte and plasma proteins, and is generally distributed

throughout the body In the case of severe wounds much more of the infused fluid, including red cells, escapes into the wound than elsewhere In the extremity from which a tourniquet has been removed after many hours, much of the fluid escapes into the leg, which can be seen to swell still more as the fluid is given The same is true in experimental peritonitis If fluids are given, one can recover far more fluid from the peritoneal cavity after a given interval than when no fluid has been given Therefore, in the presence of extensive tissue injury, with or without infection, if blood volume deficits persist in spite of massive fluid therapy, it seems to me one can assume that much of the infused fluid is oozing out into the wound

Burch What about the red cells?

Fine We have not studied the red cells in peritonitis extensively, but enough to say that the loss is not severe The same is true in tourniquet shock, in which the hematocrit is greatly increased

Burch The subjects also received red cells

Fremont-Smith However, these people subsequently had an operation in which we do not understand what occurred, and then they died, so quite a lot happened to them after these large infusions of blood before any examination could be made to determine where the blood was Is that a fair statement, Dr Howard?

Howard Yes I agree with Dr Fine's comments about the changes in blood volume after the administration of plasma in tourniquet shock and peritonitis In our experience with the peritonitis patients, they ran a typical course of hemoconcentration and plasma loss This is by no means characteristic of the extremity wounds One simply cannot make serial measurements of leg volumes in casualties who are coming through from the field in shock from an extremity wound

Burch I wonder whether you weighed those patients?

Howard I have not said, at any time, that the transfused blood was within the patient We tried repeatedly to measure blood volume loss, but never obtained a blood volume loss measurement to account for the amount given However, in the operating room I feel that is not a good measurement

Knisely There is one more possibility which I should like to suggest In circumstances where the blood is agglutinated in great masses, I have seen under the microscope and grossly in the lungs, mesenteric vessels, veins of the extremities, and arteries, that large sections of the vessels were solidly impacted with red cell masses, just as the intestine can be impacted with feces There is no possible

way to prove that it happened in these patients, but it is something to look for in the future

Shorr: Do you know anything about the extracellular fluid space?

Howard. No

Selkurt Is your hematocrit ratio normal?

Howard It is quite high in the casualty with a severe abdominal wound I have seen it rise and not change during the slow administration of 1000 ml of dextran

Selkurt Could the possibility that fluid is filtering out through damaged tissue account for some of the loss of volume? I assume it would not account for all of it

Howard That could be so after an abdominal injury, but extremity wounds characteristically hemodilute over a period of days.

Knisely The methods commonly used for measuring hemodilution, measure only the hemoconcentration of *circulating* blood It is possible for large blood vessels, or large areas of small blood vessels, to be fairly solidly impacted with soft masses of agglutinated blood cells The loss of these concentrated, packed cell masses from the circulating blood would necessarily leave "diluted" blood circulating in the rest of the vascular system

Burton Dr Knisely, are you saying that all of our methods measure the circulating volume, and not the total volume?

Knisely We must face the fact that many of the clinical tests depend upon methods which have been developed and validated during studies of normal physiology If areas of blood vessels are impacted with concentrated red cell masses, as occurs following crushing injuries, the methods for measuring "blood volume," which are adequate for the requirements of physiology, do not measure what we might assume they are measuring when we apply them to pathologic physiology Such methods do not obtain samples from impacted vessels

Fine I do not think it is quite fair to put the blood volume methods in such a bad light They are accurate, even in pathological states, if sufficient time is allowed for mixing They can be utilized even in those areas where the cells may be impacted For instance, in hemorrhagic shock in the dog, there is a certain amount of stasis in the portal bed because of vasoconstriction in the liver Even so, when a blood volume measurement is made with radio-iodo-albumin, one obtains an accurate determination of the blood volume, as judged by the volume measured plus the amount of blood removed

Burch I should like to ask Dr Fine what he meant by "accurate"?

Fine If a specimen of blood is taken from any part of the circulation, one will obtain a pretty good determination

Knisely. You say that time should be allowed for mixing However, blood taken from any part of the body will be *circulating* blood It will not be impacted blood

Fine Do you imply that the circulation is obstructed?

Knisely. I should say it is plugged

Fine In that case, I should expect rupture of the vessels

Knisely Rupture does not necessarily happen

Fine There might be increasing distention, because the arteries are still filling the veins, and something tremendous ought to happen We have not observed any evidence of such a process

Shorr In which structures, Dr Knisely, is this most likely to occur?

Knisely It is not possible to make a statistically valid answer But impactions of vessels do appear in human beings following crushing injuries, and it can be observed in the small vessels of the bulbar conjunctiva of the eye Such impactions also occur in various parts of animals following crushing injuries But it is not possible to make statements concerning which organs or tissues will have the largest number of such impactions I would, of course, expect them to occur frequently in the lungs

Shorr Do you think the small vessels of the eye, which are exposed to external temperature, are good indicators of this process?

Knisely Microscopic observation of the eye permits one to see a statistically valid sample of the circulating arterial blood Following crushing injuries to, say, the human leg, one can see masses of agglutinated blood cells going down all the arterial vessels of the human eye One can also see some of the masses plugging up the vessels, but this does not tell us which other parts of the body have vessels which are plugged Other methods must be developed to permit widespread observations within the bodies of men Certainly, microscopes can be focused into many parts of human bodies which are open for necessary surgery In animals, we have looked into transilluminated portions of the outer surfaces of organs within the abdominal cavity, such as intestines, mesenteries, liver, etc , and in all of these one sees that the *circulating* blood is agglutinated equally, and that the agglutinations are equal to those which can be observed in the vessels of the bulbar conjunctiva of the animal at the same time

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rhage or sludge The outlet valves of the liver close tightly, forcing the great portal reservoir to store so much blood that failure of venous return occurs IV Sludge shock initiated experimentally without hemorrhage Thick sludge forms wherever blood flows past crushed or burned tissue, the whole circulating blood changes to a stiff sludge causing reduced flow rates through small vessels all over the body This causes stagnant anoxia of endothelium which results in plasma leakage and vessel plugging which cumulatively cause failure of venous return V Spasm of pulmonary artery The above have been observed From autopsy reports on human anaphylactic death, it is also possible to deduce VI Spasm of veins between brain and thorax

Fine· What I have said I believe applies also to septic shock

Heymans Do you have any information on cardiac output?

Howard No

Heymans Cardiac output would show what amount of blood was really circulating In irreversible shock in dogs, when large amounts of blood are given, the blood pressure first rises and then goes down again, the circulating blood volume is at a low level

Burton What are the possible dangers of overtransfusion pushing people from the hypodynamic level into heart failure, as emphasized by Professor J McMichael of the Postgraduate Medical School of London, England (5,6), and many other people? Is it possible that in people who have been anesthetized, homeostasis of blood pressure is knocked out, and there is a danger of pushing them into heart failure by giving them more blood? The blood pressure has not risen to the normal level

Howard I see your point very well, and I assure you we have discussed it week in and week out and have felt, because of clinical and autopsy findings, that it was seldom a real danger The venous system was seldom full in these patients, in fact most of them were constricted In general, they responded to continued transfusion, and with the cessation of transfusion had a drop in pressure Remember, I said that originally we could restore the blood pressure After operation we restored their pressure, occasionally, with further transfusion, but once that pressure had fallen to zero, we never saved one patient

Decompensation is used as synonymous with shock in the accepted sense It does not imply an intrinsic failure of the circulatory machinery, as indicated by the fact that hypertension may develop after partial replacement of the blood volume It is a failure of the body to compensate for the massive insult

Our studies have confirmed the fact that hypotension will develop preoperatively after a blood loss of from 25 to 30 per cent of the

These observations were made in rhesus monkeys with malaria, in dogs following crush injuries, and in dogs following severe burns.* A solid impaction will be found in dogs or monkeys with severe crushing injuries I have also observed a few cases following burns in man, where the impacted vessels were very numerous

Burch It may be seen in the retinal and scleral vessels in sickle cell anemia These cells can become markedly impacted

Acheson Are there any correlations between this phenomenon of impaction and changes in the lymph or blood flow in the area?

Knisely. I have no information on that

Burch. The blood pressure does not change even though there is impaction in the lung

Knisely. Dr Fine, I think we should always make certain that a method which is effective in physiology can be applied to pathology.

Fine I still assert that blood volume methods are valid in hemorrhagic shock We have examined the tissues of animals dying of this, and have not observed solid obstructions to blood vessels in the liver or spleen We have made a very careful study of these and other organs

Shorr What about tourniquet shock?

Fine We have not examined the tissues in tourniquet shock

Dawes Did the animals have long-term transfusions?

Fine All of these animals had transfusions. If these vessels are blocked, they must be unblocked by the use of transfusions

Knisely In hemorrhagic shock alone, with no crushing, the blood does not agglutinate in man That is another kind of shock, with different mechanisms Therefore, we are not entitled to an argument on this point

EDITOR'S NOTE Dr Knisely would like to add the following to his remarks at the conference

> Some kinds of shock can be separated experimentally (4) In the clinic, several kinds may be occurring simultaneously in one patient If, and whenever, the whole circulatory system fails, some part or parts of the system must be behaving in such a fashion as to permit or cause the blood to stop circulating Any such reaction should be detectable Kinds of failure include I Endothelial leakage which can be caused by (*a*) anoxia, (*b*) toxic substances II Hemorrhagic shock without trauma Human blood donors developed prolonged complete vessel spasms, but no sludge Reopened anoxic vessels leak rapidly III Reservoir retention shock, without hemor-

*Many of these observations have been carried out during investigations aided by a contract between the Office of Naval Research and the Medical College of South Carolina (NR 114-065)

net results of its action, including hypotension, in a patient whose sympathetic system is already active, is not infrequently a fatal one

Massive transfusion has recently been employed on a scale not previously possible in military medicine It is not always obvious why it should be necessary. We have felt sure that external loss did not approach the amounts used, yet we have seldom been able to demonstrate a large blood volume by the Evans blue, or radioactive chromium, methods In fact, one of the striking findings has been how smoothly convalescence progressed in some patients with a postoperative blood volume deficit of from 25 to 30 per cent

Table II is a summary of 60 patients requiring between 15 and 42 pints of blood during the first 24 hours after injury. Again note the high mortality after the abdominal injuries as compared to the extremity injuries In Table III, note the higher incidence of serious renal failure after abdominal injuries in the same 60 patients

Fine. Have you any data about the incidence of infection among the abdominal injuries? That might account for the greater mortality in those cases than from extremity wounds.

TABLE III

Resuscitation of Battle Casualties—Patients Requiring 15 or More Pints of Blood in First 24 Hours Incidence of Renal Failure

Injury	No Living Three Days or Longer	Anuria %	Oliguria %	NonOliguric Azotemia %
Abdomen	9	22%	11%	11%
Abdomen and Extremity	14	28%	0	7%
Extremity	19	0	11%	22%
Chest	1	0	0	0
Total	43	14%	7%	14%

blood volume The experience with the plasma expanders has also confirmed the fact that the margin of safety is relatively much greater in the red cell mass than in the blood volume That is to say, the body cannot long tolerate a rapid loss of 50 per cent of the blood volume, but can tolerate, when necessary, a rapid loss of 50 per cent of the red cell mass if the total blood volume is maintained

As previously stated, the resuscitation of approximately 4,500 casualties was observed An adequate supply of type 0 blood was always available, and the average evacuation time was 3 5 hours In the absence of continued hemorrhage, or a wound to the central nervous system, there were no casualties whose pressure could not be restored prior to anesthesia This statement does not hold during and after anesthesia, which blocks the patient's reactivity, and may, in itself, be a lethal injury Vasoconstrictors play their chief role in resuscitation at this time, that is, when the sympathetic system is blocked by drugs Pentothal has several actions, but to the proponents of hypotensive therapy let me say that the

TABLE II

Resuscitation of Battle Casualties—Patients Requiring 15 or More Pints of Blood in First 24 Hours

Injury	TOTAL SAMPLE			Number Dying of Continued Hemorrhage	Mortality Excluding Continued Hemorrhage
	No	No Died	Mortality		
Abdomen	16	13	81%	7	67%
Abdomen and Extremities	20	10	50%	2	42%
Extremities	21	2	9 5%	0	9 5%
Chest	3	2	67%	1	50%
Total	60	27	45%	10	34%

It would also explain why creatinine is being excreted at a different rate

Howard. I think that is partially correct

Shorr I wonder whether that could be the entire explanation There is a greatly augmented creatinine excretion, which would have to result from its formation at an increased rate If it were entirely a matter of increased renal excretion of creatinine, then we would have to make the parallel assumption that increased creatinuria increases the rate of degradation of creatine to creatinine within the muscle

Heymans In abdominal injuries, there could be less creatinine liberated in the circulation, whereas in extremity wounds, there might be more

Howard. An analysis of the greater number of cases will demonstrate an increased creatinine excretion in both groups

Shorr Then this is a phenomenon for which we have no present explanation There is very little creatinine present in muscle tissue at any given moment In the course of 24 hours, in the normal healthy subject, about 1½ gm of creatine is converted to creatinine, and the latter is entirely excreted This rate of creatine degradation to creatinine is extraordinarily constant both at rest and with activity Under the circumstance that Dr Howard describes, about 8 gm of creatinine appears in the urine per 24 hours This would mean that the degradation of creatine to creatinine is now going on at an extraordinarily augmented rate We cannot "suck" this amount of creatinine out of the muscle stores because it is not there in that amount, hence, if it is really creatinine that is measured it must mean an increased rate of formation I know of no parallel situation.

Heymans The formation of creatinine is difficult to explain, but the difference in excretion could perhaps be explained

Shorr Renal excretion could account for only a very small amount of the extra urinary creatinine One of the possibilities to be considered is that Dr Howard is not actually measuring creatinine, but some other substance We must remember that the Jaffé reaction is not very specific

Howard Among 53 patients of the earlier casualties treated at the Renal Insufficiency Center, the mortality was 50 per cent In the 12 patients with wounds limited to the extremities, the mortality was 17 per cent In the 22 patients with wounds of the liver or kidneys, the mortality was 77 per cent *

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*Teschan, P E From the Surgical Team in Korea (Unpublished data)

Howard I will give you what data* we have Why this difference between the abdominal and extremity wounds? If it is a bacterial factor, it is not demonstrable by culture of the peripheral blood stream (and I emphasize our limited method), because blood cultures of 174 of the more seriously injured patients revealed an incidence of only four to eight per cent of positive cultures This incidence could not be related to the type of wound, the degree or duration of hypotension, or the prognosis

There were several striking differences between the two groups The crude indices of mortality and renal failure have been mentioned Studies have demonstrated a greater impairment of hepatic function in the abdominal group and a greater reduction of renal blood flow and glomerular filtration as measured by para-aminohippuric acid (PAH) and inulin clearance. The casualties with abdominal wounds hemoconcentrate to a remarkable extent, whereas those with extremity wounds hemodilute The casualty with extremity wounds is the one who may develop hypertension after injury

Finally, the extremity wound is associated with creatinuria, whereas the abdominal injury seldom is Both groups may have a remarkable excretion of creatinine, but the extremity wound is associated with a creatinuria.

Fremont-Smith Was that associated with a high creatinine in the blood?

Howard Only if there was renal failure

Fremont-Smith I assume it would indicate an enormously high glomerular filtrate

Howard: That may not be the explanation

Fremont-Smith If your creatinine level in the blood is normal, what other explanation would you have?

Howard There would be a question of tubular excretion

Heymans May I ask if the conditions of the circulation were controlled in these patients? Blood pressure, circulating blood volume and cardiac output would give a more complete picture than blood pressure alone

Howard I agree I believe that after abdominal injury circulation is impaired to a much greater extent than after an extremity wound

Heymans: That would perhaps explain why renal insufficiency is more marked in an abdominal injury than in an extremity injury

*Unpublished data from the Surgical Research Team in Korea

Fine You assume that too many have lost their ability to respond

Knisely: What did you routinely do to the injured man?

Howard He received penicillin intramuscularly, as soon as he reached the aid station Our studies demonstrated that although absorption had been delayed, by the time he reached the hospital there was present a blood level which is considered to be therapeutic At the hospital, he was given penicillin for a number of days postoperatively If he had an abdominal injury, or any one of the several more severe injuries, he received streptomycin, and possibly aureomycin or terramycin Gas gangrene was a most infrequent complication Wound cultures frequently demonstrated *Clostridium perfringens,* and yet in a year and a half I saw clinical gas gangrene only ten times I never saw a single death from an uncomplicated gas gangrene, but I saw one man with gas gangrene and renal failure, who died

Fine Would you say that the *Clostridia* were not responsible for death because gangrene was not present?

Howard No, let us put it this way. after the first 24 hours we seldom lost a patient, and with gas gangrene, which took longer than that to develop, we did not lose them During those first 24 hours, with hypotension and peritoneal contamination, I am not prepared to evaluate the role of *Clostridia*

Fine Are you prepared to say that because gangrene was not present, *Clostridia* were not responsible for the late deaths?

Howard They did not die

Fine If they had died, you would say they did not die because of clostridial infection?

Howard I have not had any experience with that

Fine I do not think it is fair to assume that *Clostridia* are pathogenic and lethal agents only when they produce gangrene

Howard Right They are very frequently in the wound, and they are there day in and day out

Fine: Van Heyningen (8) has described a number of clostridial toxins that have lethal effects other than gangrene

Fremont-Smith What about loss of fluid into the bandages in the wound area?

Howard It was not marked We have no concept as to how long tissue fluid was lost into the wounded tissue, and at what stage it was reabsorbed I think that is one of the things we must answer What are the changes, as to magnitude and duration, which occur in and near the wound? We are told that albumin is extruded, and

I believe that future work in support of the battle casualty should center around the control of the circulation Renal failure, and hypotension after anesthesia, were the two complications which caused the death of the greatest number of casualties Wounds of the brain, or wounds of major abdominal vessels, of course resulted in a high hospital mortality In the support of that group which we might hope to save within a foreseeable period of time, emphasis should be placed on the function of the autonomic system, the effects of the wound on the circulation, the effects of anesthesia on the circulation, and the etiology of posttraumatic renal failure

Fremont-Smith I think the extraordinary thing is that it was possible to obtain, so close to the front line, a series of observations of this sort It is something we have been longing for for many years Although the observations are incomplete, I believe the quality of the observations that were obtained is extraordinary They provide a basis for study, and the gaps may be filled in, as opportunities arise

Fine Dr. Howard, did you obtain any postmortem data?

Howard Yes, but our data are currently being analyzed All of the statements I have made, I consider to be tentative The postmortem data did not inform us as to the fate of infused blood, which was the primary thing that we were looking for They did not demonstrate marked hepatomegaly, splenomegaly, or blood in the gastrointestinal tract However, they did demonstrate some edema and frequently showed increased weight of the lungs

We saw patients die in the first 24 hours, and I cannot get out of my mind, Dr Fine, that much of what we are calling peritonitis may be abdominal trauma, and that there may be a qualitative difference between abdominal and extremity trauma This may not be due to infection, but to trauma. There may be a qualitative difference between a wound near the celiac axis, and one in the leg

Fine It makes a difference what criteria we use for the assertion that infection is or is not present For instance, if we take a large piece of liver from a dog in shock, mash it up, and put it into the peritoneal cavity of a guinea pig, the pig will die If we examine the peritoneal cavity, we will not find the usual signs of peritonitis, by *Clostridia* The animal is dead of a clostridial infection because we can prevent the death by giving clostridium antitoxin The same is true when liver mash from a dog in shock is given to another dog in shock The latter survives if given penicillin (7)

Howard. Agreed I do not wish to go on record as saying that such patients do not have peritonitis

Fine You assume that too many have lost their ability to respond

Knisely: What did you routinely do to the injured man?

Howard: He received penicillin intramuscularly, as soon as he reached the aid station Our studies demonstrated that although absorption had been delayed, by the time he reached the hospital there was present a blood level which is considered to be therapeutic At the hospital, he was given penicillin for a number of days postoperatively If he had an abdominal injury, or any one of the several more severe injuries, he received streptomycin, and possibly aureomycin or terramycin Gas gangrene was a most infrequent complication Wound cultures frequently demonstrated *Clostridium perfringens,* and yet in a year and a half I saw clinical gas gangrene only ten times I never saw a single death from an uncomplicated gas gangrene, but I saw one man with gas gangrene and renal failure, who died

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we presume that plasma is, but we know nothing about magnitude of loss, or duration of the changes

Fremont-Smith. You do think there was no loss into the bandages?

Howard. As a generalization, that would not answer our problem

Shorr Was there any difference between the reaction of the Korean soldier and that of the American soldier?

Howard· That subject was frequently discussed, and there were as many answers as observers There are no objective data on it

Nickerson. Those who work in an experimental laboratory are continually faced with the fact that anesthesia markedly depresses cardiac output without any correlation with blood pressure I wonder whether any of the men in the group who have had experience with animals have ideas as to why anesthesia *per se* depresses cardiac output?

Stead. I do not think the question should be restricted to those who have worked with animals

Burton Dr Howard, do you know of any anesthetic which operates just at the higher central levels and does not knock out all the reflexes, and so would not have an adverse effect? Did all the anesthetics you tried have this effect, or were there some that did not?

Howard That is a criticism that has been made repeatedly, but the anesthetics used in military services are rather standardized, and data on other kinds are not available

Folkow· Have you any observations concerning the changes in venous pressure? What happened to it in these cases of shock which could not be saved in spite of repeated transfusions? In animals brought to a state of irreversible shock by a prolonged period of hypotension, induced by bleeding which is followed by repeated transfusions, it seems that the venous pressure ultimately rises, which points to heart failure, rather than peripheral circulatory collapse, as the primary cause in these particular cases

Howard The visible veins did not become distended

Fremont-Smith. Did you use the ordinary heart level limit method at all for a rough approximation?

Howard Only the changes in the patient's position The veins were characteristically constricted, and in starting the transfusions, one had to use local trauma in order to distend them

Fremont-Smith You could not fill them up so that there were distended veins which would empty only when one got above the heart level?

Howard Seldom

Heymans We have performed many experiments to see what anesthetics were acting on the mechanisms of blood pressure homeostasis, because we believe that if an anesthesia knocks out or depresses this mechanism, then any other factor depressing circulation may easily induce circulatory failure

According to observations in dogs, the best anesthesia to maintain the normal mechanisms of blood pressure, homeostasis, is chloralose, which cannot be used for clinical purposes The second least depressive is nitrous oxide, and the third is ether Then there is the whole series of barbiturates However, I should say barbital, used very frequently for experimental purposes, is the least safe of any anesthesia because it knocks out all the mechanisms of blood pressure homeostasis Pentobarbital is less toxic from that point of view, but if a large amount is given to induce deep and long-lasting anesthesia, it is just as bad as barbital Pentothal, in cases in which there is no need for very deep anesthesia, is not as dangerous as the others, but still a large dose may completely knock out the physiological mechanisms of blood pressure homeostasis, and induce a condition of instability in the circulation The blood pressure may, however, still be normal

But a normal blood pressure does not mean a normal circulatory condition Quite often one forgets that It may be very abnormal, because compensation may not be available A small bleeding, or other cause, may then induce a drop in blood pressure Thus, anesthesia is an important factor in experimental investigations, and also for clinical purposes

Knisely Because these patients could always be resuscitated before they had the anesthesia, was that an indication that the anesthesia was the causative agent in making the patient's situation worse? Might they not have deteriorated anyway? It was said, if I remember rightly, that sometimes anesthesia was administered about six hours after injury

Howard Frequently, death followed in a matter of minutes

Knisely However, I should like to leave that point of the argument open for future thought Is there a possibility that part of the effect of nitrous oxide was due to the patient's being deprived of oxygen? It is rather well known that a decreased supply of oxygen to the endothelium does not help, but increases the inability of the endothelium to retain blood proteins

Years ago we used to use ether when we were trying to study the small blood vessels with a microscope For some reason we stopped using it My recollection is that it was because it altered

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Dawes: I certainly agree with Professor Heymans that barbiturates have an effect on peripheral blood flow, and that they cause peripheral vasodilation. I have always wondered why such anesthetics are used on battle casualties.

Howard. The battle casualty may have a full stomach, and therefore requires an anesthetic which does not induce vomiting.

Dawes. Is it possible that we could find a better anesthetic than those we are using at the moment? The search for new general anesthetics has not been very active recently.

Stead. In our experience, the venous pressure of all patients who do not have rupture of a large vessel can be brought back to normal by transfusion. If one pint is not effective, we give them two, three, four, or five pints. Most of the patients in the hospital have an accountable loss and replacement of blood, but every once in a while we observe exactly what Dr. Howard found: we give a patient a large quantity of blood, and then cannot find it in the body. We have not made any exhaustive measurements, but have noted that they do not seem overfilled with blood at autopsy, as do the patients with chronic congestive failure.

I think we have to agree that our techniques of measurement are not equal to the problem. In very severely injured people we see this phenomenon of putting in a great deal of blood and not finding it in the large blood vessels. However, the blood may be in plugged-up capillaries.

Fine. Those are the patients whose cardiac output falls in spite of the tremendous amount of blood they have been given. But we know where the blood goes in the dog. When dogs do not respond to transfusions, much of it goes into the splanchnic bed, because there is intrahepatic vasoconstriction. If we transfuse them via the portal vein, the belly fills with blood even though there is no leak in the perfusion system. One can recover liters of blood from the peritoneal cavity. The dog differs in this respect from man, I think, because one sees intestinal hemorrhage in a dog that dies of shock after transfusion much more often than one sees it in man.

Burch. If a vein is not distended it does not necessarily mean that the pressure within is not high. And if the veins near the heart are distended, it may not mean that total blood volume is increased. When the pathologist cuts a large vessel at autopsy and blood gushes forth, it might be that the blood happened to be shifted into the larger central vessels from the peripheral ones. Again, a person

whose central venous volume is low, may have a high total venous volume because blood may be distributed more peripherally Therefore, to obtain the venous pressure and venous blood volume, direct measurements must be made, and one must not depend on distension, or the appearance of the veins

Stead Raising the venous pressure is mechanically possible However, it does not have any therapeutic use because it does not improve the condition of the patient

Acheson One can certainly produce anoxia with nitrous oxide, but whether this happens or not is up to the anesthetists I presume they are well enough trained so as not to produce anoxia, since this is one of the cardinal tenets of the anesthetist Therefore, I would doubt that it is one of the factors With respect to induction with pentothal, I should think there are other means of induction

Zweifach In addition to the fact that anesthesia interferes with compensatory mechanisms, and thereby limits the response of the patient, there is the possibility that some form of active decompensation may set in

The effect of anesthesia on the circulation involves multiple factors From our experience with ether, I should say that the physiological effects of this agent with respect to the circulation are in large part attributable to its direct action on peripheral circulatory processes Ether clearly interferes with the capacity of the blood vessels to undergo active vasoconstriction I should guess that ether may limit the response in shock by a deleterious effect on the peripheral circulation

The experimental evidence does not favor anoxia as the mechanism involved, but rather points to specific drug effects of ether When hemorrhagic shock in the dog was carried out with various anesthetics, ether was the only agent that produced an increase in capillary permeability under standard conditions

Dawes I hope you will not underestimate its effect on reflex mechanisms

Zweifach The impairment of various systemic readjustment mechanisms should not be overlooked

Liljestrand It is, of course, impossible to get a good anesthetic effect with nitrous oxide alone, because such a high partial pressure would be needed that hypoxia would follow Although this increases the anesthetic effect, it has serious disadvantages It is possible, with a small dose of a barbiturate, to obtain a very good effect from nitrous oxide, which from many points of view is an ideal

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Heymans I agree that all anesthetics are dangerous, some more than others, and especially when the patient is in shock Local anesthesia, if it can be used, is certainly the best, because it does not interfere with the rest of the circulation and its homeostasis Of course, there is the practical problem of whether an operation can be performed with local anesthesia

There is also the matter of shortening the delay between trauma and operation, because shock is not a static condition It is a dynamic thing and represents a vicious circle At one moment the condition is reversible, but later on it may become irreversible, and then anything we do cannot save the patient

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REFLEX FACTORS IN THE REGULATION OF THE CIRCULATION

G. S. DAWES
Nuffield Institute for Medical Research
University of Oxford, England

THE CHANGES WHICH can be caused in the circulation and respiration upon injection of a chemical compound are shown in Figure 8 simply to emphasize the size of the changes. One hundred µg. of phenyl diguanide were injected intravenously into a cat, and as you can see, there was an astonishing fall of blood pressure and heart rate, and a temporary inhibition of breathing. Observations of this kind have led to the conclusion that there are a number of circulatory and respiratory reflexes which are interesting to study and which seem to be very active; the problem is to decide whether they are new ones, or whether we are looking at old phenomena in a new form.

I should like to add a word of elucidation. Although in the last five years there has been a good deal of interest in the reflexes which are caused by the injection of chemical compounds, the idea that there are in the circulation reflex mechanisms which we do not fully understand is by no means new. All that this particular work has done is to focus attention on the newer type of reflexes, if I may use that term – some of them are actually very old – rather than those in the carotid bifurcations and in the aortic arch, which have been so amply studied by Professor Heymans, and many others since his brilliant initial investigation.

Dr. Fremont-Smith said something about logic. I think the problem we are faced with is a logical analysis of all the material with which we are presented. It is extremely confusing. Thus, what I am proposing to do is to put before you a skeleton of the kinds of reflexes which control the circulation, and I hope you will add the sinews and muscles, and even cover it with a little skin. On the left side of Table IV are a number of cardiovascular reflexes, and on the right side a list of the sensory receptors which have so far been discovered, in the heart, or in the great vessels.

One of our problems is to decide to what extent the sensory receptors which we have found can explain the reflex mechanisms

anesthetic, because the effect vanishes in a few minutes. I think it would be of great advantage to try such a combination

Heymans: I agree that all anesthetics are dangerous, some more than others, and especially when the patient is in shock Local anesthesia, if it can be used, is certainly the best, because it does not interfere with the rest of the circulation and its homeostasis. Of course, there is the practical problem of whether an operation can be performed with local anesthesia

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TABLE IV

Cardiovascular Reflexes and Sensory Receptors

REFLEXES	RECEPTORS
1 Carotid sinus (and common carotid nerve) – aortic arch pressure reflex	Carotid and aortic pressure receptors
2 Carotid and aortic body chemoreflex	Carotid and aortic chemoreceptors
3 The coronary chemoreflex (Bezold effect)	Atrial types A and B (8)
4 The left heart reflex (1)	Ventricular (9,10)
5 Pulmonary depressor reflex	
6 Pulmonary depressor chemoreflex	Pulmonary?
7 The Bainbridge reflex (2,3,4,5)	
8 Extravagal reflex (6,7)	

I am not going to say anything at all about the carotid sinus pressor and chemoreceptor reflexes, because I think we are all very familiar with them, although we can learn a great deal more from studying them, as Professor Heymans has recently shown. They form a pattern of a presso-receptor mechanism which may be applicable to other types in another part of the body

There is one point I wish to draw your attention to in Table IV I have put "common carotid nerve" in brackets That is merely to remind you that Dr J H Green (11) has recently found there is a nerve in the cat which arises from the common carotid artery, a centimeter or so below the carotid bifurcations, and which comes from a pure presso-receptor area As Professor Heymans suggested at one time, this discovery brings up the question as to whether such presso-receptor areas are so restricted in their distribution as we have previously thought

Comroe There is good evidence that in unanesthetized man manipulation of the arterial wall with a blunt needle, or a needle with a hook on the end of it, will cause fainting I am not sure whether this is associated with slowing of the heart, but it certainly is related to a fall in blood pressure Do you think these arterial visceral sensory receptors are relatively insensitive parts of the same system?

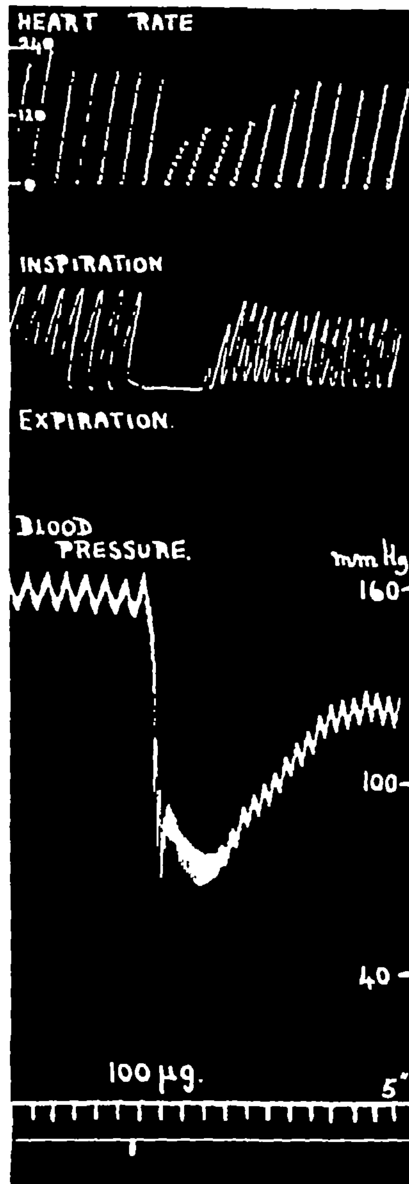


FIGURE 8 Cat, chloralose anesthesia Records of heart rate, in beats per minute, using a Thorp impulse counter actuated by the QRS complex of the electrocardiogram, of respiratory movements from a body plethysmograph, and of carotid arterial blood pressure Time in 5-second intervals At the signal mark 100 μg phenyl diguanide were injected intravenously Reprinted, by permission, from Dawes, G S Reflexes from the heart and lungs *Brit M Bull* 8, *324 (1952)*

which are known There are gaps in our knowledge, and I think that these are the interesting points, and the ones on which we should concentrate attention One must also bear in mind the possibility of differences between these reflexes in their central and efferent mechanisms I am not going to touch on those fields, because I think that the afferent mechanisms are sufficiently complex, but I hope that someone else will illuminate that side of the subject

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1 Carotid sinus (and common carotid nerve) – aortic arch pressure reflex	Carotid and aortic pressure receptors
2 Carotid and aortic body chemoreflex	Carotid and aortic chemoreceptors
3 The coronary chemoreflex (Bezold effect)	Atrial types A and B (8)
4 The left heart reflex (1)	Ventricular (9,10)
5 Pulmonary depressor reflex	
6 Pulmonary depressor chemoreflex	Pulmonary?
7 The Bainbridge reflex (2,3,4,5)	
8 Extravagal reflex (6,7)	

I am not going to say anything at all about the carotid sinus pressor and chemoreceptor reflexes, because I think we are all very familiar with them, although we can learn a great deal more from studying them, as Professor Heymans has recently shown They form a pattern of a presso-receptor mechanism which may be applicable to other types in another part of the body

There is one point I wish to draw your attention to in Table IV I have put "common carotid nerve" in brackets That is merely to remind you that Dr J H Green (11) has recently found there is a nerve in the cat which arises from the common carotid artery, a centimeter or so below the carotid bifurcations, and which comes from a pure presso-receptor area As Professor Heymans suggested at one time, this discovery brings up the question as to whether such presso-receptor areas are so restricted in their distribution as we have previously thought

Comroe There is good evidence that in unanesthetized man manipulation of the arterial wall with a blunt needle, or a needle with a hook on the end of it, will cause fainting I am not sure whether this is associated with slowing of the heart, but it certainly is related to a fall in blood pressure Do you think these arterial visceral sensory receptors are relatively insensitive parts of the same system?

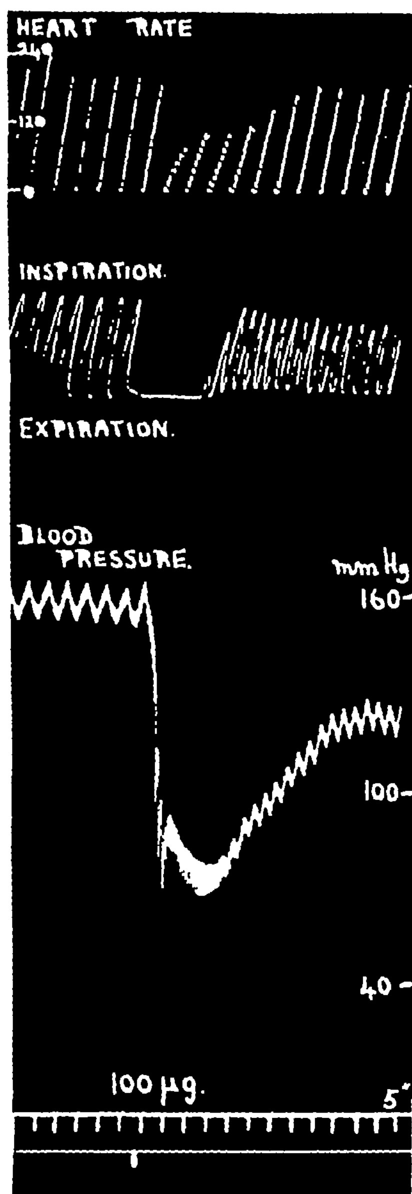


FIGURE 8 Cat, chloralose anesthesia Records of heart rate, in beats per minute, using a Thorp impulse counter actuated by the QRS complex of the electrocardiogram, of respiratory movements from a body plethysmograph, and of carotid arterial blood pressure Time in 5-second intervals At the signal mark 100 µg phenyl diguanide were injected intravenously Reprinted, by permission, from Dawes, G S Reflexes from the heart and lungs *Brit M Bull* 8, *324 (1952)*

which are known There are gaps in our knowledge, and I think that these are the interesting points, and the ones on which we should concentrate attention One must also bear in mind the possibility of differences between these reflexes in their central and efferent mechanisms I am not going to touch on those fields, because I think that the afferent mechanisms are sufficiently complex, but I hope that someone else will illuminate that side of the subject

Comroe I believe Lovén found that stimulation of sensory nerves in a limb would produce vasodilation in that limb, and an increase in systemic blood pressure, that would, of course, produce an increase of blood flow to that limb

Heymans Yes, but don't you think we have to be careful to make a distinction between physiological and nonphysiological stimulation If we talk about stimulation of a group of receptors, or of nerve fibers, we ought to know what type of stimulation we are using If we speak about presso-receptors, we ought to keep in the range of physiological stimulation, these receptors being specifically sensitive to pressure variations in the arterial or the venous side Mechanical or electrical stimulation of many receptors, including presso-receptors, or of the presso-receptor and sensory fibers, may induce many reactions other than the normal physiological ones. By stimulating these receptors, mechanically or electrically, we produce artefacts If we are not careful about making this fundamental distinction, I think we shall run into many difficulties

The so-called Lovén reflexes, which by stimulation of some nerves produce reflex vasodilation, and also reflex increase of arterial pressure, may represent an artefact, but if we had to answer the question, "What is the physiological stimulant of the receptors of these nerves, and what are they doing physiologically?" we would have a lot of difficulty. Thus, we have to make a fundamental difference between the physiological and nonphysiological stimulations of receptors, and of nerve fibers The same observation applies to the sinoaortic presso-receptors and chemoreceptors

Knisely· Dr Dawes, these are all reflexes in which the afferent side is somewhere in the vascular system, so the discussion up to this point concerns physiological factors which are well known We have repeatedly placed pressure recorders in various sections of a single animal In a dog, anesthetized lightly or heavily, we put pressure recorders in the aortic system, the venous system, either the femoral vein or the vena cava, the portal system, the pulmonary vein, and the pulmonary artery One can sometimes get all of those in without much, if any, bleeding

The human being is the only experimental animal that we accidentally shoot, burn, or otherwise put into shock with no anesthetic at all After severely burning experimental animals that have been lightly anesthetized, the recordings go into violent, irregular, rhythmical high or low pressure to such an extent that all the writing points of the recorders go completely off the paper That is certainly not homeostasis, but something quite different The somatic affer-

Dawes. I do not know, but I am prepared to speculate I think it is very unlikely that it is the same type of mechanism as the presso-receptor mechanism of the carotid artery, and the aortic arch.

Heymans: As Dr Dawes said, these receptors (confining ourselves to presso-receptors of the carotid sinus and the aortic arch) are somewhat of an old story, but as is true of many old stories, up to now it has been far from complete Before going into the details of all the vascular receptors, perhaps a question has to be raised as to how these receptors sensitive to pressure variations, let us say to arterial pressure variations, start to act, and how they regulate the systemic arterial pressure

The second question to be asked is: what are the thresholds of these different presso-receptors? As Dr Dawes said, years ago it was shown that there are presso-receptors in different areas They are in the arteries of the thoracic area and the mesentery, and I would not be astonished if, in looking for them in other areas such as in the common carotid artery, and by noting the action potentials of some nerves connected with these areas, that we would see some receptors responding to pressure variations I believe that they are around everywhere, but perhaps in the whole arterial vascular system their function, with respect to the blood pressure regulation, may be quite different The presso-receptors occupy different levels There are main presso-receptors first of all comes the carotid sinus and then the aortic arch In addition, there are receptors situated in some other areas As to their role and function, I think some of them regulate, reflexly, the local and regional distribution of the blood related to pressure in a given area

Dawes Have you any specific evidence for such a reflex mechanism? I know that this suggestion has often been made, but I have never seen any evidence for it which has been really convincing

Heymans: There is indeed evidence If the pressure is changed in a mesenteric artery, vasomotor reflex responses are induced These reflexes, however, do not affect the systemic arterial blood pressure The vasomotor tone of the spleen and kidneys react to changes in pressure in the mesenteric artery It is a segmental reflex adaptation of circulation and vasomotor tone, related to pressure changes in a given area (12,13,14)

Liljestrand Dr Lovén, who was the first professor of physiology at the Caroline Institute, found a local dilation of blood vessels and a general rise in blood pressure when he stimulated certain afferent nerves

Heymans: Don't you think they may be produced at the spot where the receptors are placed?

Dawes. That remains to be proved

Acheson: With regard to the definition of terms, I think we have an analogous situation when we talk about "applied science" and "pure science" These are not good terms. Perhaps, we should say "programmatic research" and "curiosity research" It seems to me all these curious reflexes are particularly interesting because we do not know what they do, although they represent mechanisms which are there We discuss this subject because we are curious about it and that is the situation which often leads to creative research The physiological or "normal" aspect is useful, so long as we keep its limitations in mind

Fremont-Smith: If we could answer the question "With respect to what?" when we use the words "normal" or "pathological," it would help It seems to me we often generalize, when we need to specify. There isn't any such thing as "normal" in a meaningful sense until we define it with respect to certain things which we measured and found were normal The same is true of "pathological" or "abnormal"

Nickerson I think we are using the term "abnormal" in two senses One in the sense of something which is not normal to the smoothly functioning organism, but which can nevertheless arise within the organism as a result of its inherent potentialities The release of ATP, and of serotonin during blood coagulation, are examples Both can arise from within the organism, but do not normally circulate in a free form

The second definition of the term "abnormal" refers to something completely foreign to the organism, and which is present only because an investigator puts it there I am not quite sure in which sense we should use the term "abnormal" here, but on the whole I think we have been using it in the latter sense This is a distinction we must keep in mind because of the very nebulous line between the normal and abnormal developing within the organism itself

Comroe Dr Dawes and I have discussed this matter of definition many times in the last month, and I think that I induced him to put into the definition the idea that a chemoreceptor reacts to chemical changes that occur in its normal environment, or in certain pathological states My reason for this is that I believe the carotid and aortic bodies respond particularly to abnormal states. I do not believe anoxia is normal to an individual, and yet anoxia is certainly the prime stimulant to the carotid body

ents stimulated by the burns are separate from the physiological afferents.

Dawes: But you have to take the physiological afferent nerves into account first

Knisely. Of course

Dawes I think Professor Heymans would agree to keeping the term "chemoreceptors" for those sensory receptors which are normally excited by chemical changes in their environment, that is to say, normal chemical changes, such as those of oxygen or CO_2 partial pressure, pH, and so on, or in the tongue and the nose, changes in the environment induced by substances which are inhaled or swallowed under normal conditions I do not think we should use the term "chemoreceptor" to indicate any sensory receptor which is excited by injection of a foreign substance, because we now know that many other types of receptors which we should regard, from the physiologist's point of view, as stretch or pressoreceptors, can also be excited by the injection of foreign chemical substances

Until we know more about these reflexes which are excited by the injection of chemical substances, it is convenient to call them, as a group, "chemoreflexes" That does not mean that their afferent mechanism is due to the excitation of chemoreceptors "Chemoreflex" is a useful term provided we know its limitations I hope we all agree on that point

Fremont-Smith You mean, then, that "chemoreflexes" is a broad term including reflexes which may be induced by receptors that are not normally chemoreceptors?

Dawes Precisely

Burton May I suggest, perhaps facetiously, that we might call them "pharmacological receptors" until we know their physiological role?

Heymans It is often difficult to make a distinction between a pharmacological and a physiological stimulation The carotid and aortic bodies are provided with receptors, let us say "chemoreceptors" sensitive to physiological chemical stimulants and also to drugs But some other receptors, located in the coronary and pulmonary circulation, seem to be sensitive only to certain drugs, although their sensitivity to ATP and serotonin has also been submitted

Dawes Professor Heymans, you would not seriously suggest that either ATP or serotonin normally circulate in the blood in sufficient quantities to excite these receptors?

Heymans. Don't you think they may be produced at the spot where the receptors are placed?

Dawes. That remains to be proved.

Acheson. With regard to the definition of terms, I think we have an analogous situation when we talk about "applied science" and "pure science." These are not good terms. Perhaps, we should say "programmatic research" and "curiosity research." It seems to me all these curious reflexes are particularly interesting because we do not know what they do, although they represent mechanisms which are there. We discuss this subject because we are curious about it and that is the situation which often leads to creative research. The physiological or "normal" aspect is useful, so long as we keep its limitations in mind.

Fremont-Smith. If we could answer the question "With respect to what?" when we use the words "normal" or "pathological," it would help. It seems to me we often generalize, when we need to specify. There isn't any such thing as "normal" in a meaningful sense until we define it with respect to certain things which we measured and found were normal. The same is true of "pathological" or "abnormal."

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Comroe. Dr. Dawes and I have discussed this matter of definition many times in the last month, and I think that I induced him to put into the definition the idea that a chemoreceptor reacts to chemical changes that occur in its normal environment, or in certain pathological states. My reason for this is that I believe the carotid and aortic bodies respond particularly to abnormal states. I do not believe anoxia is normal to an individual, and yet anoxia is certainly the prime stimulant to the carotid body.

However, I do not think we should call any receptor a chemoreceptor simply because it responds to one of these peculiar chemical compounds that have never been found in normal man, or in tissues in pathological states. On the other hand, if we are going to admit to our definition ATP and serotonin, which may conceivably be present in the circulating blood or locally, and which are known to stimulate certain chemoreflexes, then I think we must satisfy ourselves that these compounds are present in contact with the sensory receptors in sufficient concentration, in these pathologic states, to cause excitation Otherwise, the chemicals are activating chemoreflexes, but not true chemoreceptors

Alexander On the other hand, I am impressed by the picture we have seen in Figure 8 Many of these reflexes are associated with stimulation of receptors in the vicinity of the lungs The response is characterized by apnea, plus cardiovascular changes, leading temporarily to a relative stagnation of the circulation The possibility should be kept in mind that these may be definite mechanisms to protect the body against noxious agents coming in by way of the respiratory tract Hence they would be definitely homeostatic mechanisms regardless of how completely foreign the stimulus might be in a given situation

THE CORONARY CHEMOREFLEX

Dawes I think it would now help the discussion a great deal if we presented a few facts I can start by summarizing the evidence for the separate existence of reflexes 3 and 4, in Table IV, and that will perhaps give us something more specific to talk about

Liljestrand Is there any evidence that apnea after those substances is really a reflex effect? As the blood pressure sinks, one might expect apnea simply as a result of hypoxia If blood is rapidly withdrawn, there will be apnea

Dawes There is ample evidence, but since this is a conference primarily on circulation, I was hoping we could restrict it to the circulatory effects If we get into respiratory reflexes, we shall find that they are even more difficult

Liljestrand I just mentioned it because that is one of the characteristics.

Dawes I think the following figures will give us a basis for discussion

Figure 9 gives the evidence for the Bezold effect, or coronary chemoreflex In the future I shall call this the "coronary chemoreflex." In the heparinized and anesthetized cat, if its chest is opened, and the bent glass tube seen in Figure 9 is inserted through

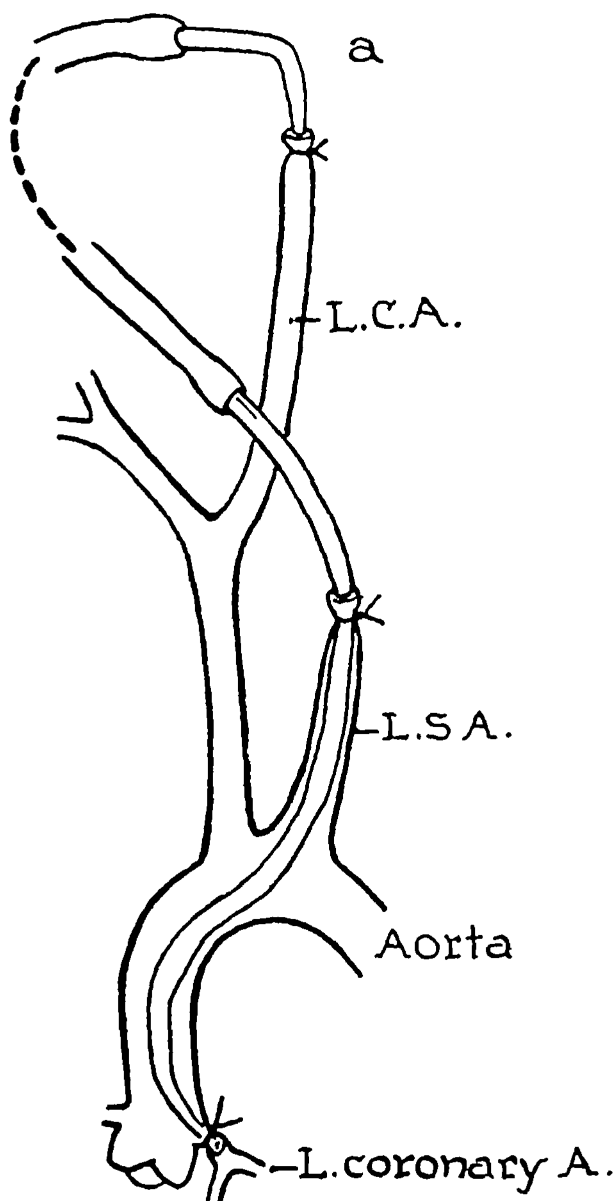


FIGURE 9 Diagram of preparation for injection into the left coronary artery in cats The left carotid artery (*L C A*) is connected by a cannula (*a*) and rubber tube, to a glass tube passed down the left subclavian artery (*L S A*), and tied into the mouth of the left coronary artery The animal is given heparin to prevent clotting The chest may then be closed Reprinted, by permission, from Dawes, G S Studies on veratrum alkaloids, receptor areas in coronary arteries and elsewhere as revealed by use of veratridine *J Pharmacol & Exper Therap* **89**, 325 *(1947)* Williams & Wilkins

the left subclavian artery (*L S A*), and passed down into the mouth of the left coronary artery, and if the central end is connected to the left carotid artery (*L C A*), drugs may then be injected into the coronary artery (15) The chest can then be closed

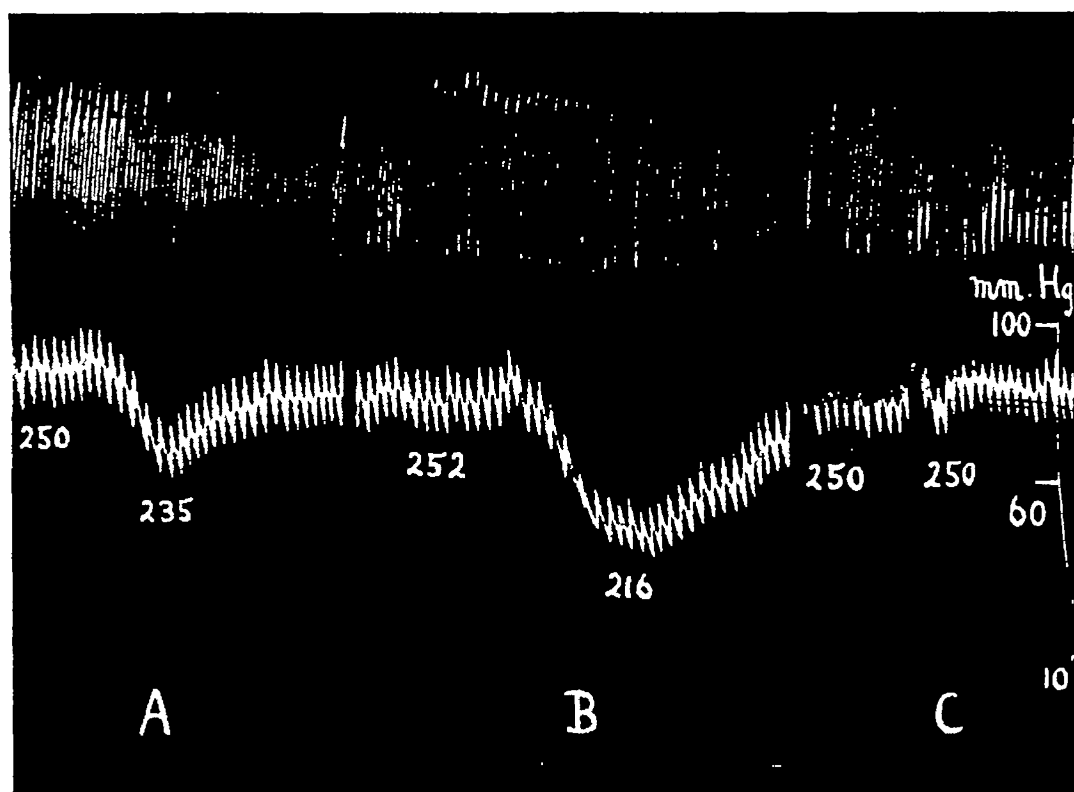


FIGURE 10 Cat, chloralose anesthesia Records of respiratory movements (above), recorded by a modification of Gaddum's method (16), and of blood pressure (below), from the carotid artery The heart rate, in beats per minute, was measured from the electrocardiogram, and is also indicated on the record At *A*, 0 25 μg veratridine, and at *B* and *C*, 0 5 μg veratridine were injected into the left coronary artery by the method illustrated in Figure 9 Between *B* and *C* the vagi were cut in the neck

Figure 10 shows that when a small dose of veratridine (0 25 μg at *A*) is injected into the left coronary artery, a fall in blood pressure and heart rate is observed (16) A larger effect is seen on giving 0 5 μg at *B* Between *B* and *C* the vagi were cut, so there was no longer any effect when the same dose that was given at *B* was repeated at *C* Thus, there are some receptors in the coronary circulation which can cause a fall in blood pressure and heart rate

In the dog the coronary arteries are larger and one can inject into individual branches Figure 11 shows the preparation from the left side diagrammatically The left circumflex coronary artery has been cut. The peripheral end has been cannulated from *b* and joined to a carotid artery, and the central end cannulated in the same way from *c* Injection into the peripheral end, that is, into vessels largely supplying the left ventricle but also other structures, causes a fall in blood pressure and heart rate Injection into *c*,

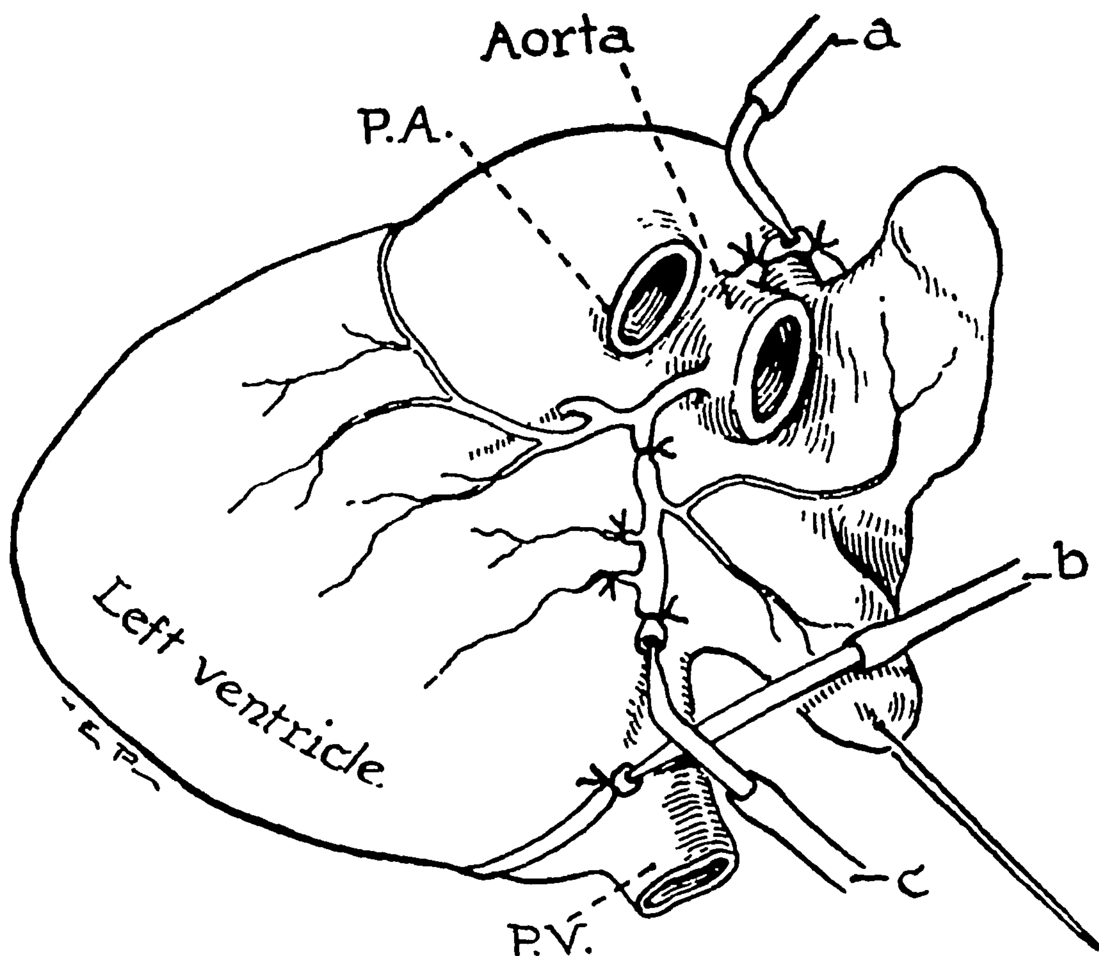


FIGURE 11 Left lateral view of preparation for simultaneous perfusion of the coronary arteries of the dog Cannulae are inserted in the right coronary artery (*a*), the peripheral end of the left circumflex (*b*), and its central end (*c*), which now feeds only the left superior atrial coronary artery They are connected to a carotid, or internal mammary artery, by a rubber tube, the dog is given heparin to prevent clotting Reprinted, by permission, from Dawes, G S Studies on veratrum alkaloids, receptor areas in coronary arteries and elsewhere as revealed by use of veratridine *J Pharmacol & Exper Therap* **89**, *325 (1947)* Williams & Wilkins

which supplies mainly the atrial appendages, does not cause a fall in blood pressure and heart rate An injection of veratridine into the right coronary, *a*, in the dog does not cause a fall in blood pressure and heart rate

By this kind of experiment, the conclusion has been reached that it is the arterial supply of the muscle of the left ventricle that causes this phenomenon, although I would add a note of caution These experiments do not exclude the possibility that there may also be an action on sensory receptors in the atria All we can say is that there are definitely sensory receptors in the arterial supply to the left ventricle Whether these are in the ventricular tissue, we do not know

Burch If a small segment of coronary artery is isolated without allowing the substance to reach the smaller arterioles or capillaries, would the results be the same?

Dawes We have not done that experiment All we have done

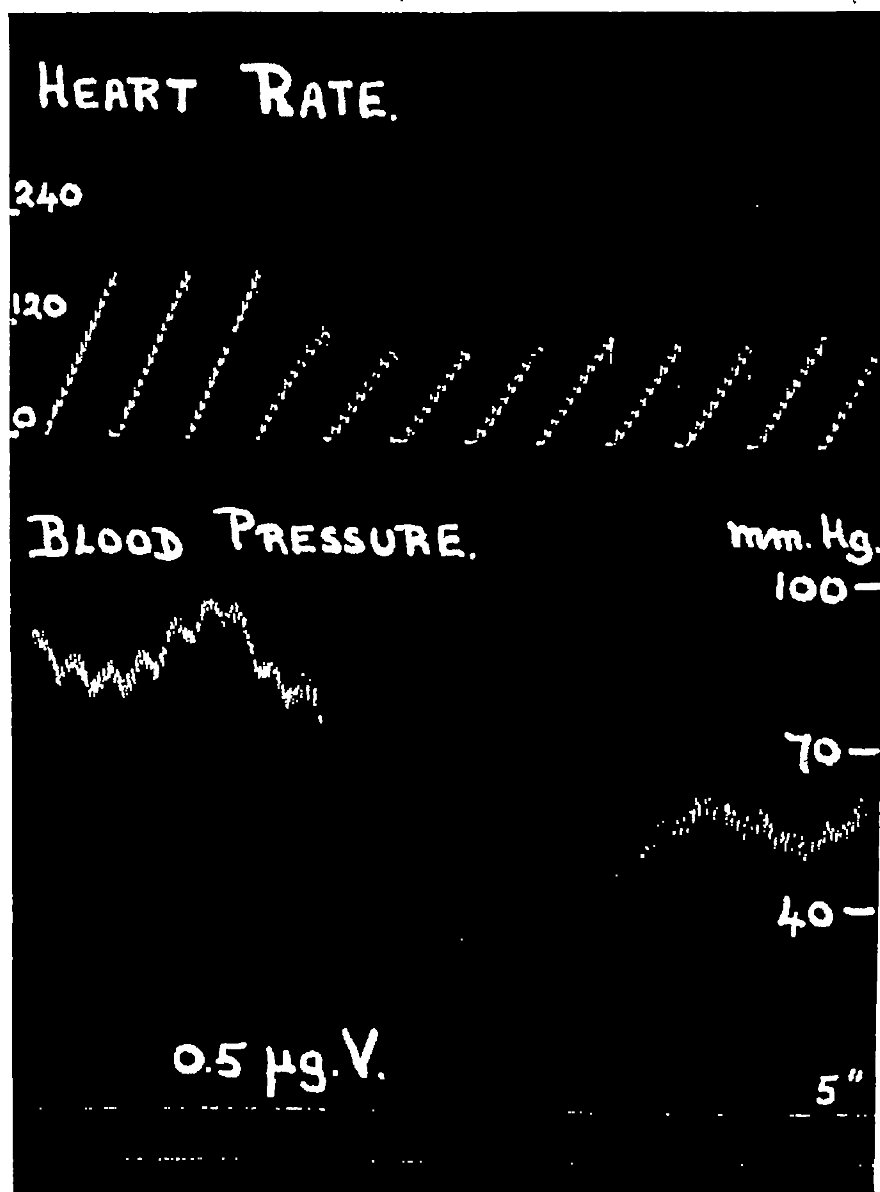


FIGURE 12 Dog, chloralose anesthesia Record of heart rate (above, as in Figure 8), and of femoral arterial pressure (below) At the signal, 0 5 μg veratridine was injected into the peripheral end of the left circumflex coronary artery, using a preparation similar to that shown in Figure 11 (*b*) The minimal effective dose of veratridine on intravenous injection is about 20 times greater Time in 5-second intervals Reprinted, by permission, from Dawes, G S Reflexes from the heart and lungs *Brit M Bull* 8, 324 (1952)

is to raise the pressure in the arteries, and then we do not obtain a response.

Burch You have never limited it to a segment of artery?

Dawes No

Moe. You have essentially done it in *c* of Figure 11

Dawes Yes, I suppose so However, it could be objected that that is the wrong place We have not isolated a segment of, say, the left circumflex coronary artery I think it would be technically difficult to do

Burch Did you determine the temporal relationship from the time of injection to the time of response?

Dawes Yes

Burch. Is it due to circulation elsewhere?

Dawes I should say so. There are two reasons for believing that the receptors must be in the area of distribution of the coronary arteries first, because of the latent period, which is a matter of a second or two after injection, whereas the coronary circulation time is certainly more than that, secondly, the fact that the response may be obtained with a dose of veratridine, from 0 1 to 0 5 μg , injected into the coronary vessels, which is effective neither on injection into the cavity of the left ventricle, nor on intravenous injection.

Figure 12 shows a response to 0 5 μg, of veratridine, injected into a dog weighing about 10 kg You will notice that the dose is fantastically small, and the effect is very large

Figure 13 illustrates an experiment on a cat, in which we perfused the celiac axis (17) At 1·23 p m we gave an injection of 10 μg of veratridine, intravenously You see that there was an increase in outflow as indicated by a rise in the upper record, and a decrease in perfusion pressure, indicating peripheral vasodilation

Richardson Dr Dawes, would you describe in a little more detail the technique you used, and the significance of the curves in your illustration

Dawes The upper record is the flow into the celiac axis, the center is perfusion pressure of the blood pumped into the celiac axis, and the lower one is the mean arterial blood pressure of the whole cat You see that here there is evidence of reflex peripheral vasodilation In Figure 13, the two records on either side, at 1 07 and 1 40 p m , show the effect of cooling the vagi to 7½° C on this response, which is abolished Therefore the reflex response, of which the afferent path lies in the vagi, consists partly of bradycardia, and partly of peripheral vasodilation

Burch If a small segment of coronary artery is isolated without allowing the substance to reach the smaller arterioles or capillaries, would the results be the same?

Dawes We have not done that experiment All we have done

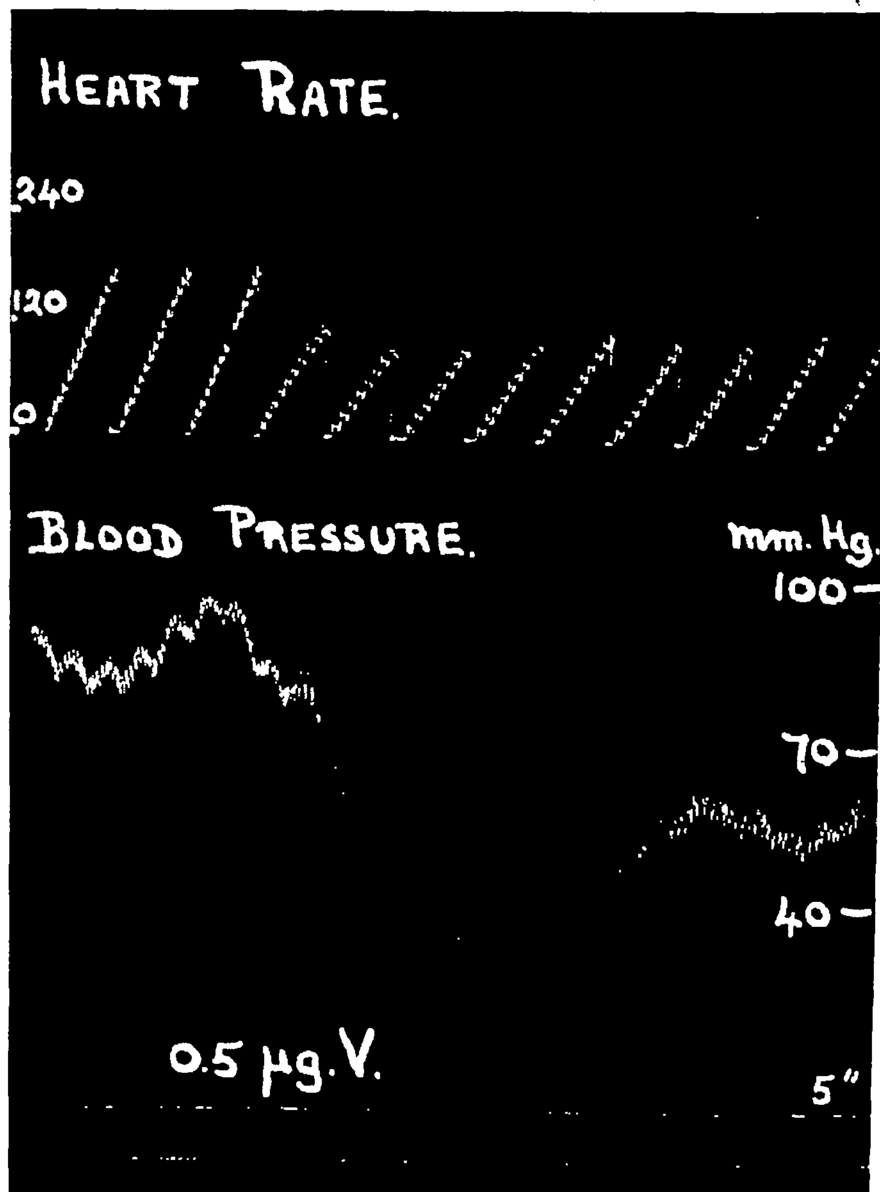


FIGURE 12 Dog, chloralose anesthesia. Record of heart rate (above, as in Figure 8), and of femoral arterial pressure (below) At the signal, 0 5 µg veratridine was injected into the peripheral end of the left circumflex coronary artery, using a preparation similar to that shown in Figure 11 (*b*) The minimal effective dose of veratridine on intravenous injection is about 20 times greater Time in 5-second intervals Reprinted, by permission, from Dawes, G S Reflexes from the heart and lungs *Brit M Bull* 8, *324 (1952)*

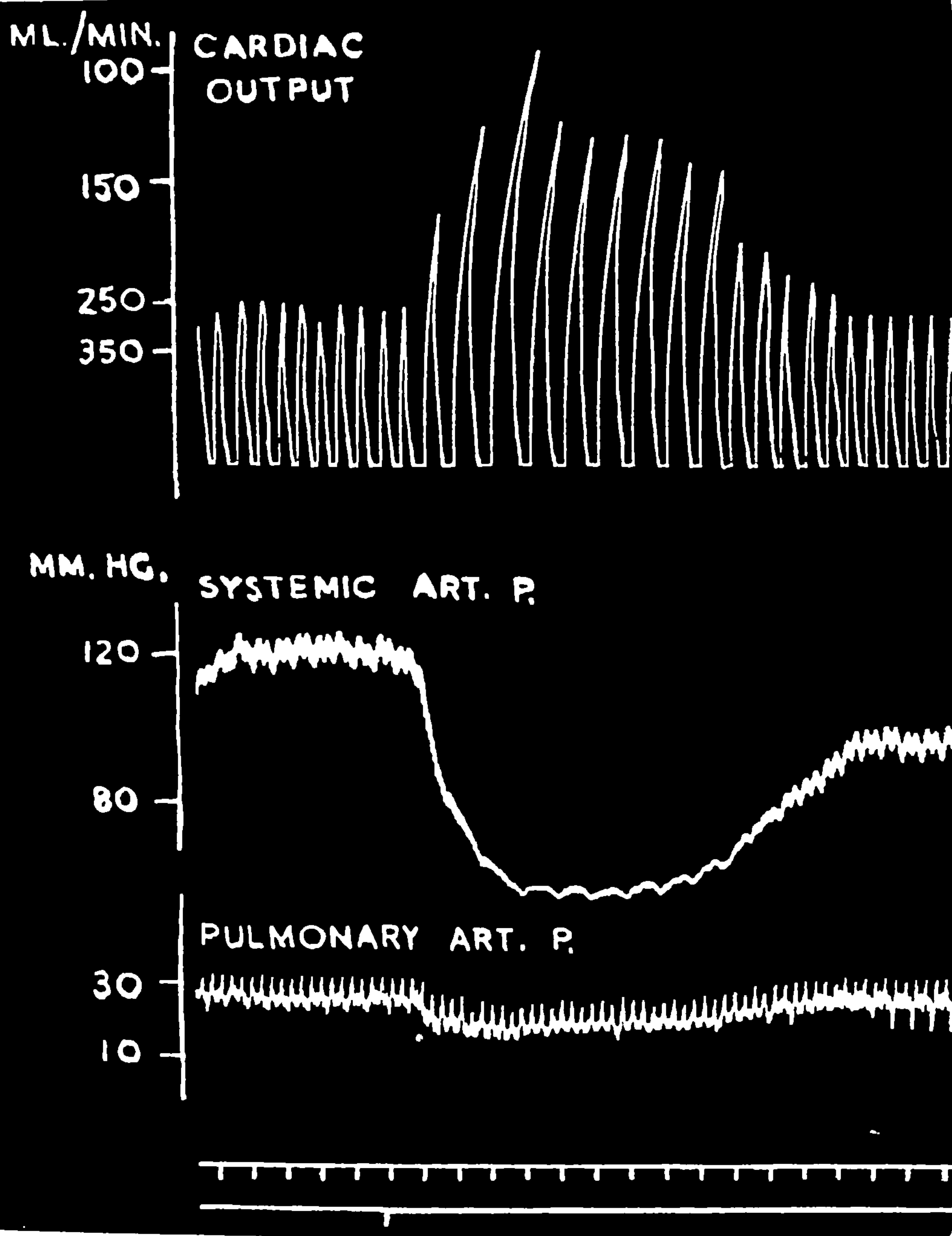


FIGURE 14 Cat, chloralose anesthesia, chest open, artificial ventilation Records of cardiac output (above) measured by a density flowmeter in the pulmonary artery, of systemic and pulmonary arterial pressures (below) At the signal mark, 20 μg veratridine were injected intravenously

flowmeter (18) The center record is of arterial blood pressure, and the lower is of pulmonary arterial pressure You will see that on intravenous injection of veratridine, there was a very great decrease in cardiac output Thus, on the efferent side there are

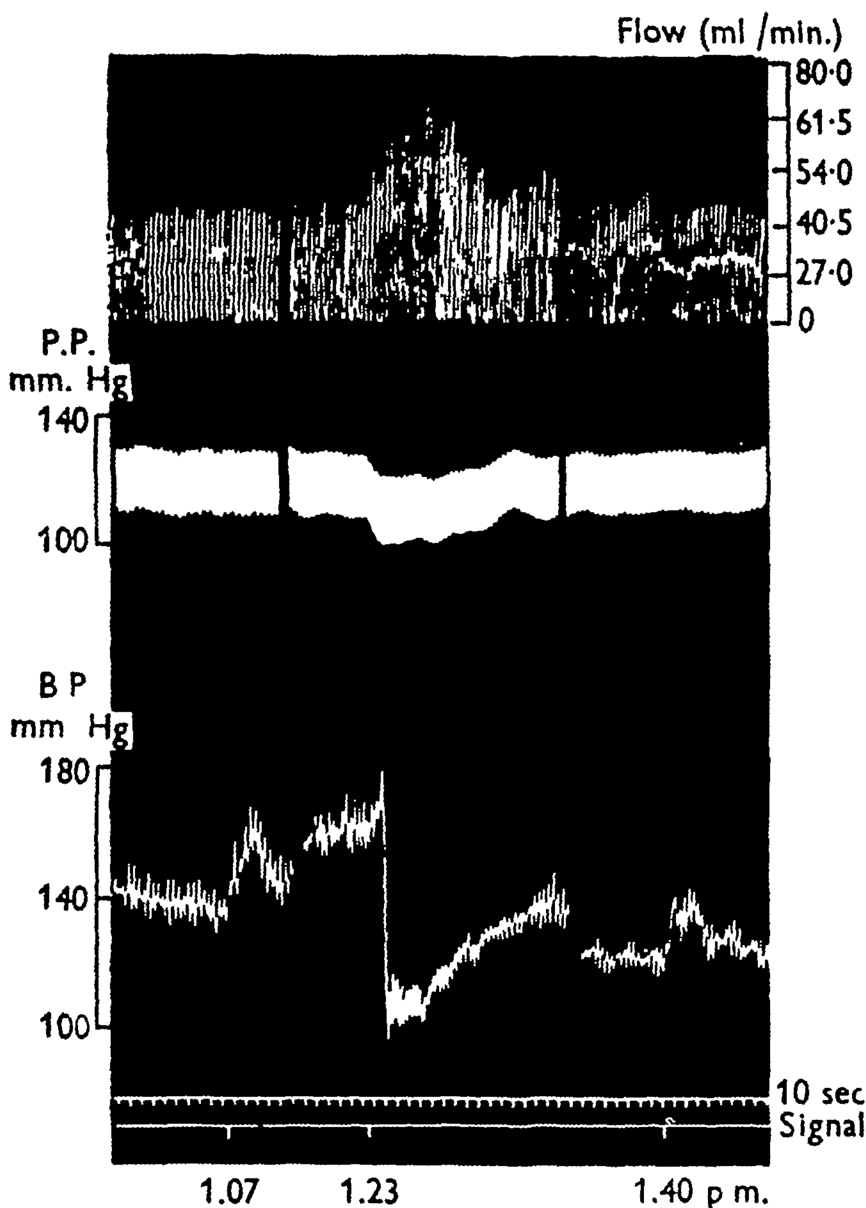


FIGURE 13 Cat, chloralose anesthesia Record of blood flow through celiac axis (above), perfusion pressure (center) and arterial blood pressure (below) Injections of 10 µg veratridine intravenously at each signal mark At 1 07, both vagi were cooled to 8°C, and at 1 40 to 7½°C, abolishing the reflex vasodilation to be seen at 1 23 p m Reprinted, by permission, from Dawes, G S, Mott, J C, and Widdicombe, J G Respiratory and cardiovascular reflexes from the heart and lungs *J Physiol* **115**, 258 (1951) Cambridge Univ Press

Figure 14 is a record from an experiment performed by Mrs G Barer and Dr E Nusser* The cat was anesthetized with chloralose, and the chest was opened The upper record is of flow through the pulmonary artery, recorded with a direct measuring

*Unpublished data

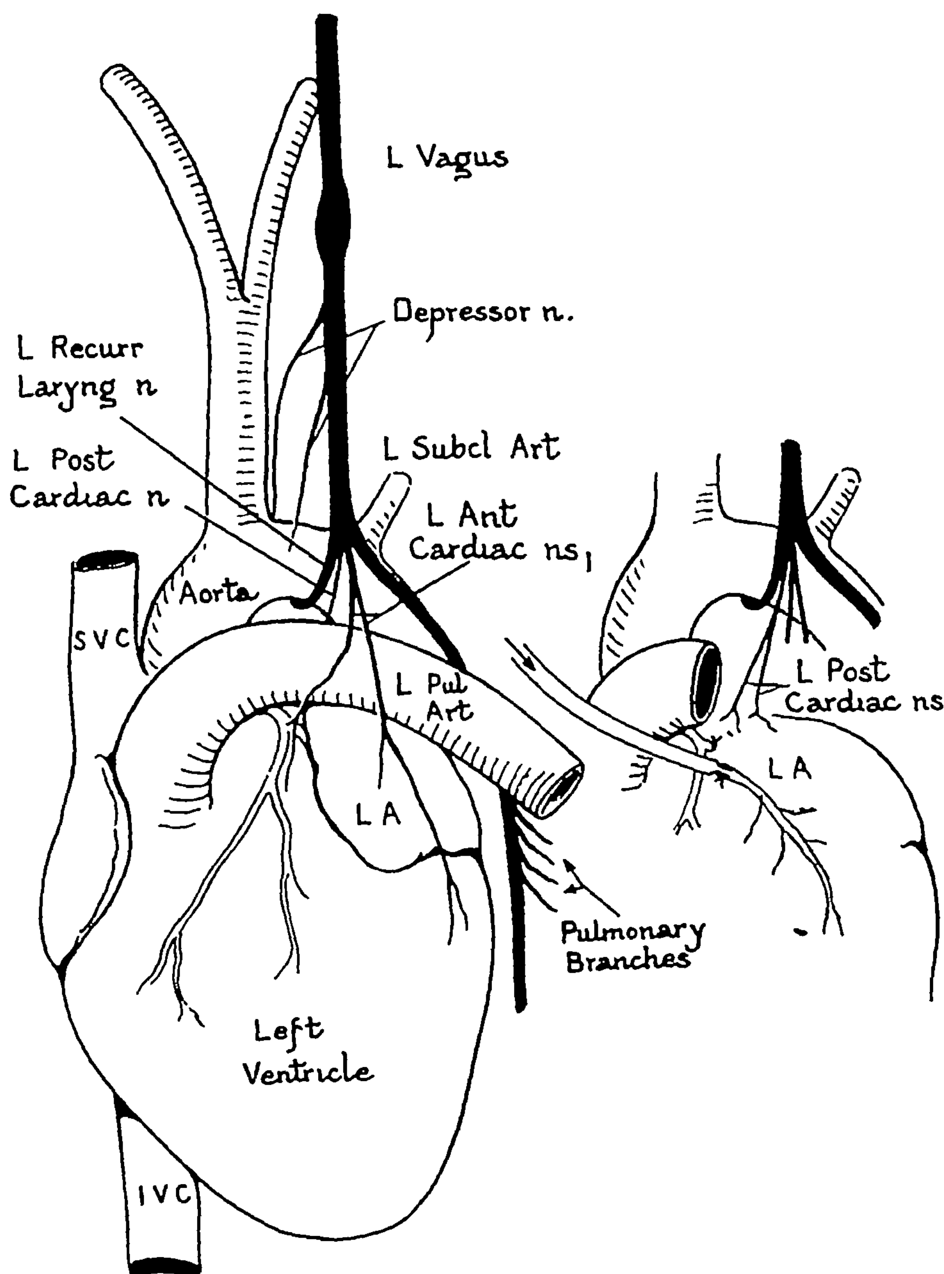


FIGURE 16 Anterior view of the heart to show the distribution of the principal branches of the left vagus The insert shows the disposition of the left posterior cardiac nerves in relation to the left pulmonary artery and left atrium (L A), the left circumflex coronary artery has been cannulated Reprinted, by permission, from Dawes, G S , and Widdicombe, J G The afferent pathway of the Bezold reflex the left vagal branches in dogs *Brit J Pharmacol* **8**, *395 (1593)*

Figure 15 is a diagram of the distribution of the right vagus nerve to the heart of the cat If the left vagus is cut, the distribution in the right vagus of the afferent fibers may be studied One has to cut all the nerves marked *II* and *III* in the figure to abolish

these two mechanisms: bradycardia, and therefore a decrease in cardiac output, and secondly peripheral vasodilation As to the afferent pathway, we have a little more information

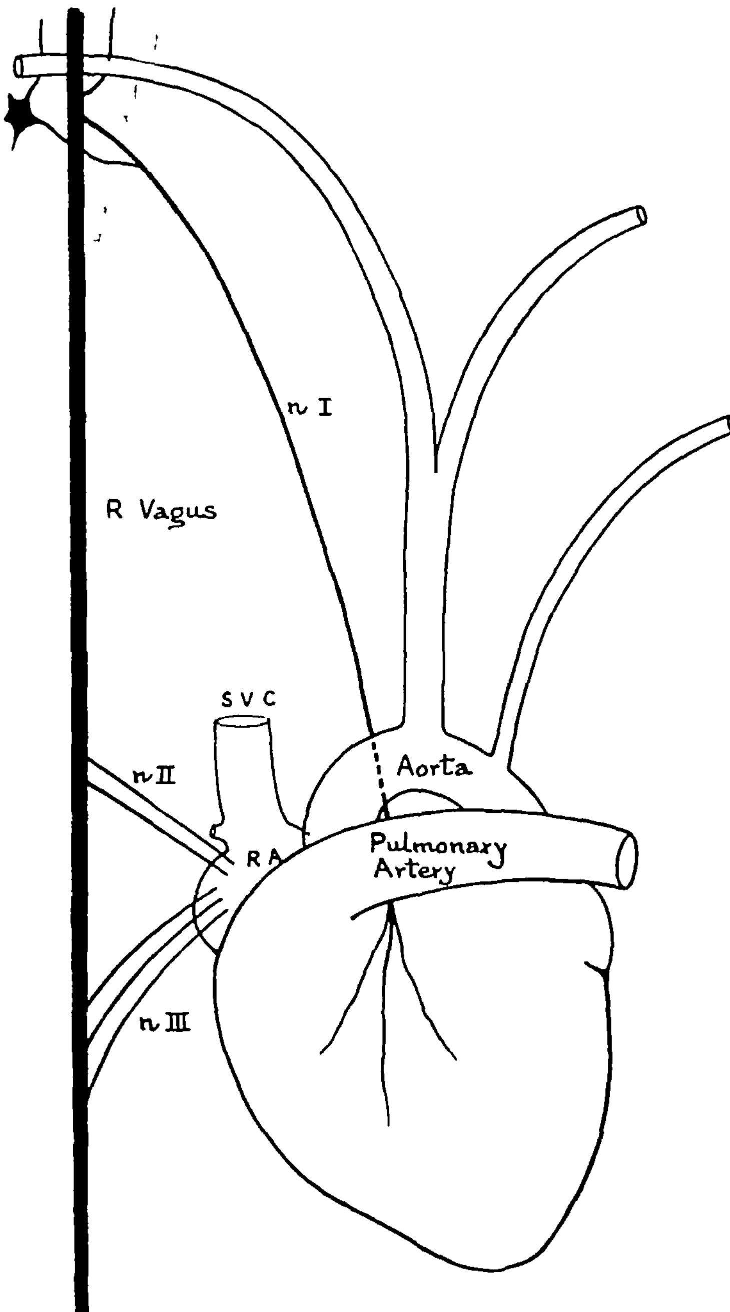


FIGURE 15 Diagram of the distribution of the cardiac branches of the right vagus in the cat Reprinted, by permission, from Jones, J V The afferent pathway of the Bezold reflex the right vagal branches in cats *Brit J Pharmacol* **8**, *352 (1953)*

about their distribution It has been suggested that they join either the depressor nerves or the left recurrent laryngeal. No one, however, has produced convincing single fiber records from them in the dog, and until that is done, I do not think we can be sure where they are situated Dr. Comroe studied their distribution in one or two animals

Comroe I have done a great many dissections in this area, and it is my belief that the aortic body fibers run from the recurrent laryngeal nerve very close to the aortic wall, because the aortic body is within a millimeter of the aortic wall. Therefore, it would be quite separate from the fibers to the left atrium if they were cut lower down

Heymans Dr Comroe, do you believe that after cutting the aortic nerves, the aortic chemoreceptors are still present?

Comroe The nerves from the aortic body go almost directly into the recurrent laryngeal right near the aorta, and they would still be intact if the nerve were cut, say, a few millimeters farther down

Heymans. How can we locate the spot where the compound is acting?

Moe By injection into the circumflex artery, I think

Dawes Yes, the cannula is inserted into the peripheral end of the left circumflex coronary artery

Comroe Furthermore, the reaction is entirely different *qualitatively* from the reactions that occur from stimulation of the aortic body

Heymans Yes, but according to the observations of Dr Dawes, the aortic chemoreceptors are stimulated by the compounds he investigated

Comroe The physiological reaction to stimulation of the aortic body is that of hypertension and hyperpnea, not of hypotension and apnea

Heymans I remember the histologic work of Dr F. De Castro (21,22,23) on the blood supply of the aortic bodies According to him, the coronary artery gives off some branches going to the aortic body

Dawes Not in the dog, Professor Heymans

Comroe In the cat, very definitely

Heymans Yes Did somebody look for it in the dog?

Comroe Yes

Heymans I should like to have a clear-cut picture of the experimental condition, so as to know if these compounds are acting on

the response (19) They are nerves which run to the atria, but are widely distributed When those nerves are cut, one also cuts the efferent cardioinhibitory nerve fibers to the heart Therefore, one cannot always be sure, in taking any particular branch of the vagus to the heart, whether the afferent nerve fibers are in it It is difficult to ascertain just where the afferent nerve fibers run What we really want to know is what the physiological stimulus is, and the use of electrophysiological methods of study seemed to offer our best hope of solving this problem

Figure 16 shows the situation in the dog, which surprisingly is somewhat easier If the vagus on the right side of the dog is cut and veratridine is injected into the left circumflex coronary artery, one obtains a fall in blood pressure without any fall in heart rate (20) We think this is due to our having cut almost all of the efferent cardioinhibitory nerve fibers in the right vagus, which is convenient because now we can go ahead and look for the afferent nerves on the left side, without the complication of cutting efferent cardioinhibitory fibers

What we found in a number of experiments was that the reflex was not abolished if we cut the aortic depressor, left recurrent laryngeal, or the left cardiac nerves which run *over* the left pulmonary artery and are distributed to the left atrium and the left ventricle This puzzled us a great deal until we observed that there were other small vagal branches, such as the left posterior cardiac nerves

In order to get at these, the left pulmonary artery must be divided The animal then survives on its right lung, which it can do perfectly well Then we find one, two or three small branches which run over the arch of the aorta, beneath the left pulmonary artery, and enter the left atrium Where they go after that, we do not know When these left posterior cardiac nerves are cut, the reflex is abolished

Heymans What about the aortic body chemoreceptors in this situation? Are they still present after the nerves are cut?

Dawes I should have mentioned that We know the aortic depressor nerves because we have recorded the characteristic action potentials from them In the dog there are always two, sometimes three, depressor branches of the vagus fairly high up, running toward the brachiocephalic artery and then down to the aortic arch When these depressor nerves are cut, the coronary chemoreflex is still present

As to the aortic chemoreceptor nerves, we do not know so much

about their distribution It has been suggested that they join either the depressor nerves or the left recurrent laryngeal No one, however, has produced convincing single fiber records from them in the dog, and until that is done, I do not think we can be sure where they are situated Dr Comroe studied their distribution in one or two animals

Comroe I have done a great many dissections in this area, and it is my belief that the aortic body fibers run from the recurrent laryngeal nerve very close to the aortic wall, because the aortic body is within a millimeter of the aortic wall Therefore, it would be quite separate from the fibers to the left atrium if they were cut lower down

Heymans Dr Comroe, do you believe that after cutting the aortic nerves, the aortic chemoreceptors are still present?

Comroe The nerves from the aortic body go almost directly into the recurrent laryngeal right near the aorta, and they would still be intact if the nerve were cut, say, a few millimeters farther down.

Heymans. How can we locate the spot where the compound is acting?

Moe· By injection into the circumflex artery, I think.

Dawes Yes, the cannula is inserted into the peripheral end of the left circumflex coronary artery

Comroe Furthermore, the reaction is entirely different *qualitatively* from the reactions that occur from stimulation of the aortic body

Heymans Yes, but according to the observations of Dr Dawes, the aortic chemoreceptors are stimulated by the compounds he investigated

Comroe The physiological reaction to stimulation of the aortic body is that of hypertension and hyperpnea, not of hypotension and apnea

Heymans I remember the histologic work of Dr F De Castro (21,22,23) on the blood supply of the aortic bodies According to him, the coronary artery gives off some branches going to the aortic body

Dawes Not in the dog, Professor Heymans

Comroe In the cat, very definitely

Heymans Yes Did somebody look for it in the dog?

Comroe. Yes

Heymans I should like to have a clear-cut picture of the experimental condition, so as to know if these compounds are acting on

the area of the coronary artery, and not on the aortic body chemoreceptors

Dawes I think I can assure you of this

Heymans I am not quite sure

Comroe Professor Addison (24,25) made complete serial sections of this whole area in the dog, and found that the arterial blood came from the arch of the aorta in practically every animal. In the cat it was entirely different, it came from a branch of the coronary artery

Alexander I should like to raise the question as to how we should describe the anatomical course of these afferent nerves For example, working on the cervical trunk higher in the neck, we can usually identify the depressor nerve anatomically and confirm its identity by observing that its action potentials correlate with the variations in arterial blood pressure However, if we dissect through the vagus and the sympathetic trunk, we find, here and there, scattered fibers which, when their action potentials are recorded, are found to behave exactly as depressor fibers That gave me the impression that, in addition to the depressor nerves which can be identified anatomically, there are also scattered depressor fibers that get lost in the vagus

Dawes Certainly And there is one other point If nicotine is injected into the left circumflex coronary artery, there will be a fall in blood pressure and heart rate, which is entirely different from the rise in blood pressure and increase in heart rate which is obtained on excitation of the chemoreceptors of the aortic or carotid bodies I think that altogether excludes the possibility that this artery supplies the aortic chemoreceptors

Heymans I am sorry, but I do not see why, because nicotine, acting on the aortic and carotid bodies, induces reflexes of bradycardia and a fall in arterial blood pressure That is a typical reaction which you mentioned

Comroe· Not on the aortic body In that case I have never observed bradycardia or hypotension, but marked hypertension, vasoconstriction, and tachycardia

Dawes I should agree with that

Heymans I am sorry, but our first experiments on chemoreceptors were done on the aortic preparations and there nicotine induced reflex bradycardia, which also happened when nicotine was injected into the carotid body circulation Therefore, I do not think the aortic and carotid bodies behave in such an opposite way There must be some other reason why bradycardia was not observed

Comroe I think I know the reason, Professor Heymans In your original experiments you used a heart-aorta preparation If nicotine is injected into a heart-aortic preparation, two groups of receptors are stimulated consecutively, and apnea and bradycardia are observed, which are followed by hypertension and hyperpnea However, if the injecting catheter is removed from the left ventricle, and inserted into the ascending aorta, injecting the chemical agent very close to the point where the artery joins the aortic body, then one no longer observes apnea and bradycardia, but pure hypertension and hyperpnea With the heart-aortic preparation, both of these effects are obtained, but with the so-called aortic preparation, one would get only the aortic body reflex With the coronary preparation, only the coronary chemoreflex would be observed

Heymans. It is possible, but I still do not believe the aortic and carotid bodies behave in such an opposite way in reacting to nicotine, because in the case of any other compound, they respond in the same manner I am quite sure the variation in this case is due to the experimental conditions, and not to a fundamental difference in behavior of these two bodies

Dawes. Professor Heymans, I should like to tie you down to a definition of what you mean by the aortic body in the dog Would you give us, first, what you think is its anatomical localization and second, some idea of what the effect of a normal chemical stimulus to it is?

Heymans I did not investigate the anatomical localization of the aortic body Dr De Castro (21,22,23), and Dr J F Nonidez (26,27,28) have performed such investigations Dr Comroe has done quite a lot of experiments on the localization of the aortic body in dogs, and I believe the anatomists, physiologists, and pharmacologists, who have worked on the aortic body, quite agree with him on its localization in dogs and cats

Dawes Where is it in the dog?

Comroe I should say it was between the wall of the ascending aorta and the pulmonary artery A small artery usually arises from the ascending aorta, and attached to it, about a millimeter from its origin, is the tiny group of cells which we know as the aortic body Serial sections of this region show the artery leaving the arch of the ascending aorta, breaking up into minute branches and going into the aortic body In the cat, the aortic body would be somewhere in the same vicinity, but it would receive its blood supply from a branch of the coronary artery

Dawes If we cannulate the left circumflex coronary artery, or

the area of the coronary artery, and not on the aortic body chemoreceptors

Dawes. I think I can assure you of this.

Heymans: I am not quite sure

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tion regarding where the sensitive structures are located, and the type of response obtained by stimulating them.

Comroe: This is an extremely difficult area in which to work, and I think Dr Dawes is to be congratulated upon carrying it this far.

Bozler Has information been obtained by studying action potentials?

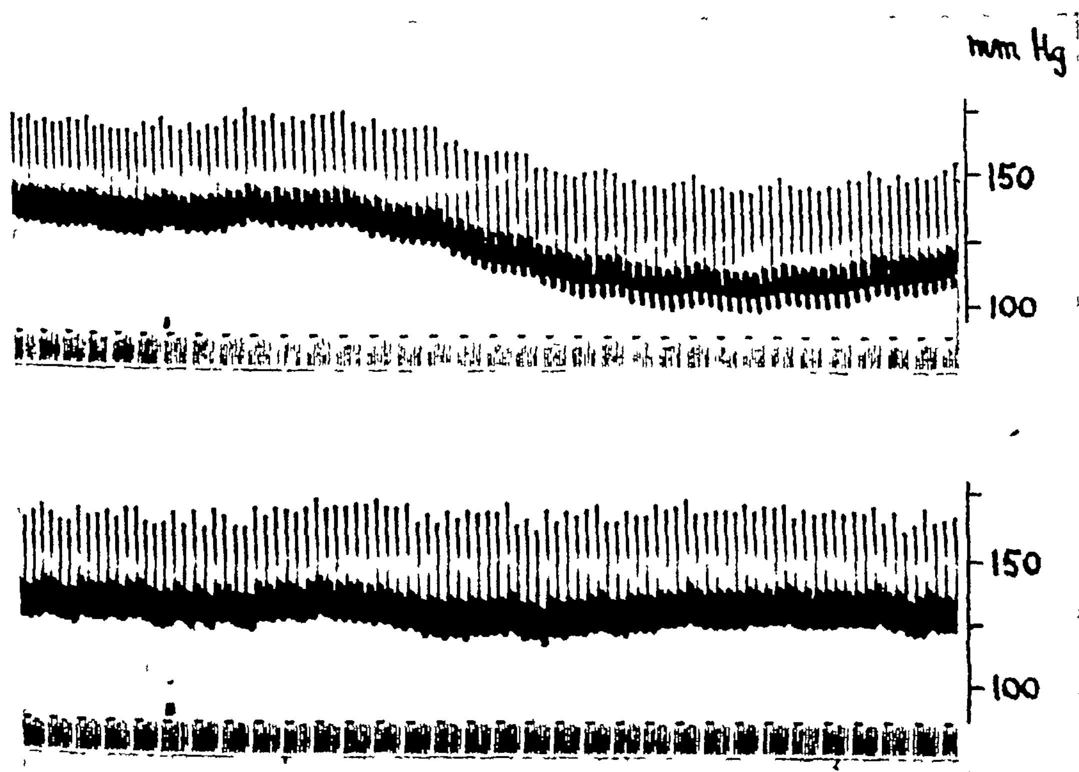


FIGURE 17 Dog, pentobarbital anesthesia Right vagus cut in the neck at the beginning of the experiment Condenser manometer records of femoral arterial pressure (above), signal and time markers (0 1 and 1 0 seconds) below At each signal mark, 1 0 μg veratridine was injected into the peripheral end of the left circumflex coronary artery, using a preparation similar to that shown in Figure 11 (*b*) Between the upper and lower records there was a ten-minute interval, during which the left posterior cardiac branches of the vagus were divided Note that there is no evidence of bradycardia even in the upper record, because the right vagus (in which most of the cardioinhibitory fibers run) is already cut Reprinted, by permission, from Dawes, G S, and Widdicombe, J G The afferent pathway of the Bezold reflex the left vagal branches in dogs *Brit J Pharmacol* 8, *395 (1953)*

Dawes Figure 17 shows the fall of blood pressure on injection of veratridine into the left circumflex coronary artery, the fall of blood pressure before section of the nerve, and its abolition after

a branch of it, and inject veratridine into it, a fall in blood pressure and heart rate is obtained. I cannot conceive how a drug injected into the left circumflex coronary artery could possibly affect the aortic body. I think we have to consider two distinct anatomical areas, the aortic body, and something in the left ventricle which is reached by an injection into the coronary vessels.

Burch. Are aberrant bodies ever found inside the heart?

Dawes. I do not know of any histological evidence for this, do you?

Heymans. There is an historical description of the paraganglia in the heart by Goormaghtigh and Pannier, (29) suggesting that these structures could be provided with chemosensitivity.

Referring to your question, Dr. Burch, it is quite possible that these so-called "pharmacological receptors" – if you do not like the name "chemoreceptors" – may be situated close to the paraganglia. These paraganglionic structures lie close to the coronary artery.

Dawes. Dr. Comroe, do you think that the anatomical localization of these paraganglia could be such that they would be reached by injections of this kind into the peripheral end of the left coronary artery?

Comroe. Paraganglia have been described by various authors in relation to most of the areas around the atria and ventricles. Each author has placed them in a slightly different place in different species. In my opinion, paraganglia have to be ruled out as a site of these sensory receptors. However, I do think that some of the injections into the left ventricle probably reach areas where there are no known paraganglia. In short, I do not think that paraganglia are excluded, but I think that the left ventricular injections are probably made into areas where there are none. That does not mean that the drug may not reach them higher up.

Heymans. There is the possibility that there are some structures where these receptors may be situated. Perhaps we are wrong, but we have to keep it in mind.

Burch. That is why it would be helpful if we could isolate a segment of a coronary artery. If such an experiment were possible, we might isolate the receptors closer to the artery.

Nickerson. I think there are two questions which we have to consider. The first is the location of receptors for particular agents. The second calls for additional information, but does not in any way detract from the importance of the first, and that is what these receptors look like. Whether they are paraganglia is another matter, and does not in any way add or detract from the specific informa-

tion regarding where the sensitive structures are located, and the type of response obtained by stimulating them

Comroe This is an extremely difficult area in which to work, and I think Dr Dawes is to be congratulated upon carrying it this far

Bozler Has information been obtained by studying action potentials?

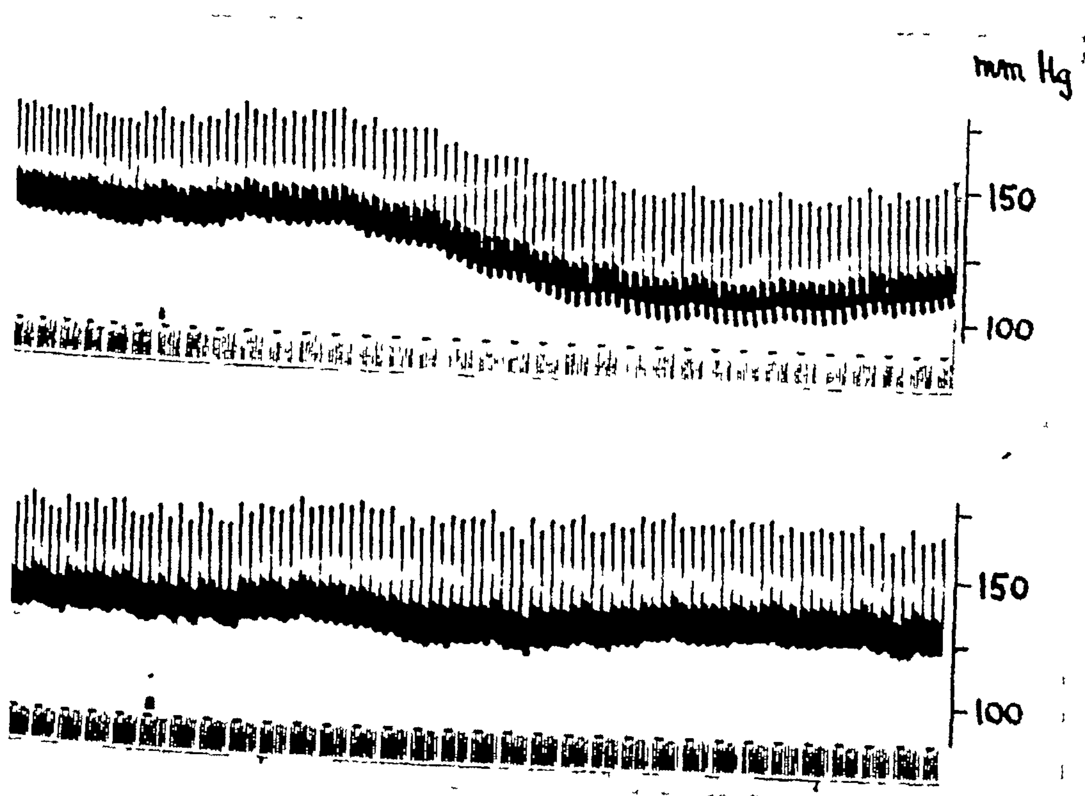


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section of the nerves shown in Figure 16 (the left posterior cardiac nerves) We did try to see what could be found in these nerves, and all we obtained was evidence of atrial receptors (20) Figure 18 shows a characteristic pattern of discharge The upper lines are

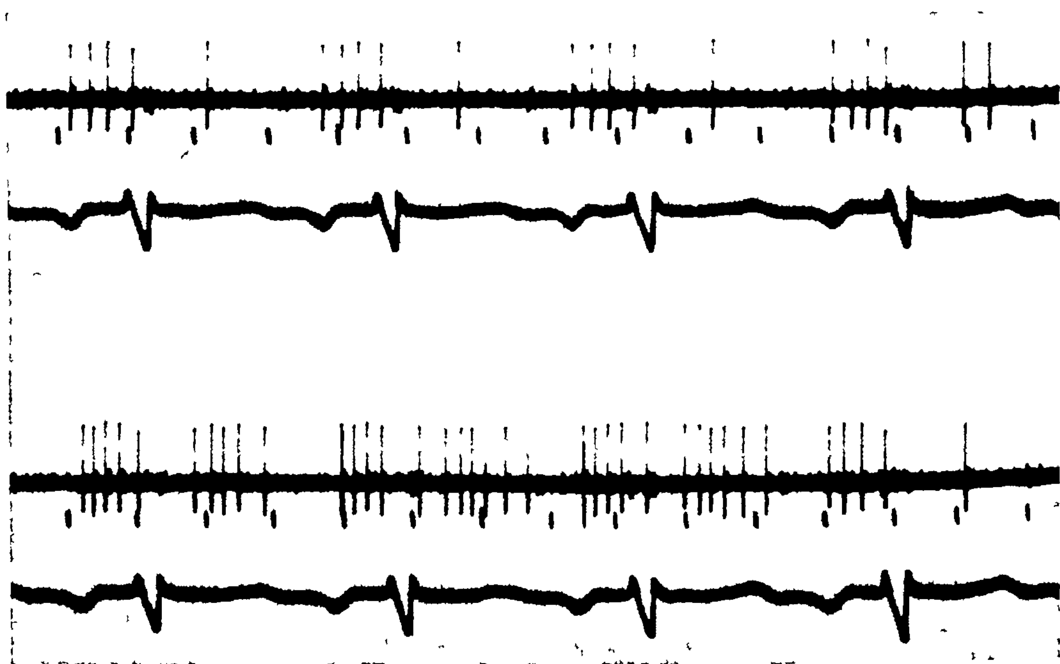


FIGURE 18 The upper lines are records of action potentials recorded from the left posterior cardiac nerves, time marks in 1/10 second intervals The lower lines are the record of the electrocardiogram The discharge varies with the phase of respiration, as shown in the top and bottom halves of the figure Reprinted, by permission, from Dawes, G S, and Widdicombe, J G The afferent pathway of the Bezold reflex the left vagal branches in dogs *Brit J Pharmacol* 8, 395 (1953)

the records of single fiber preparations from the left posterior cardiac nerves, the lower are of the electrocardiogram The top half of the figure shows one phase of respiration, and you may observe that there are four bursts between the P and the QRS complex The bottom half of the figure shows a different phase of respiration, and one obtains more discharges after the QRS complex

Heymans Are these receptors sensitive to pressure?

Dawes They are almost certainly atrial receptors. These are very characteristic

Burch Did the heart stop?

Dawes. We have not stopped a heart

Heymans: Dr Dawes, are these action potentials related to fibers

connected with presso-receptors, or with chemoreceptors, and what are the data for considering the fibers as coming from the chemoreceptors and not from presso-receptors, which we know are located in the same area?

Dawes I think they all come from presso-receptors.

Heymans Do they respond to drugs, also?

Dawes I shall come to that in a minute Figure 19 shows another

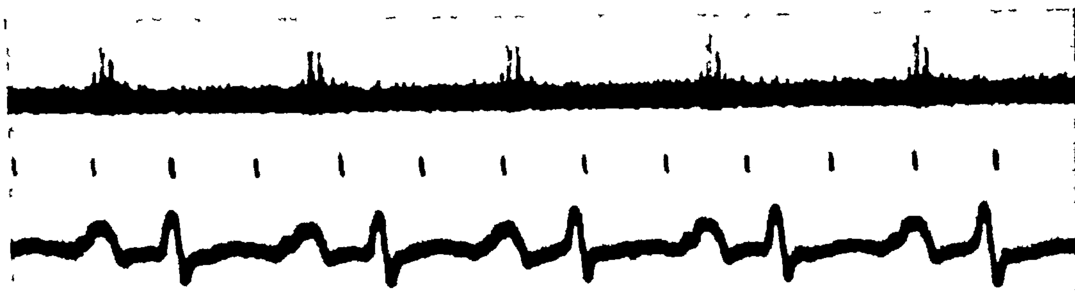


FIGURE 19 Records as in Figure 18 to show a fiber which discharges only between the P and QRS deflections of the electrocardiogram Reprinted, by permission, from Dawes, G S, and Widdicombe, J G The afferent pathway of the Bezold reflex the left vagal branches in dogs *Brit J Pharmacol* **8**, *395 (1953)*

type of afferent nerve fiber in the left posterior cardiac nerves, from which we see only a burst of action potentials in time with the P wave When we found these, we thought, "Well, this is fine All we have got to do is inject some veratridine and we shall see these nerve fibers sensitized and firing continuously" However, in the many experiments in which we injected veratridine, we never found that these fibers were excited

We have then a curious situation The nerve comes up from the left atrium The only types of nerve fibers that we have been able to detect in that section have this cardiac rhythm, but they are not excited by an injection of veratridine However, on three occasions and in two different dogs, we did hear a great increase in background activity on injection of veratridine That was regarded as evidence that fibers of an unknown type were discharging continuously at a very high frequency* It encourages us to believe that we were on the right nerve, but we do not know anything about the type of receptor

This emphasizes a particular characteristic of the vagus nerve it is rather like an iceberg Only one-tenth of it (the large fibers) is above the surface, the other nine-tenths are below

*Compare this with the work of Jarisch and Zottermann (30) on cats

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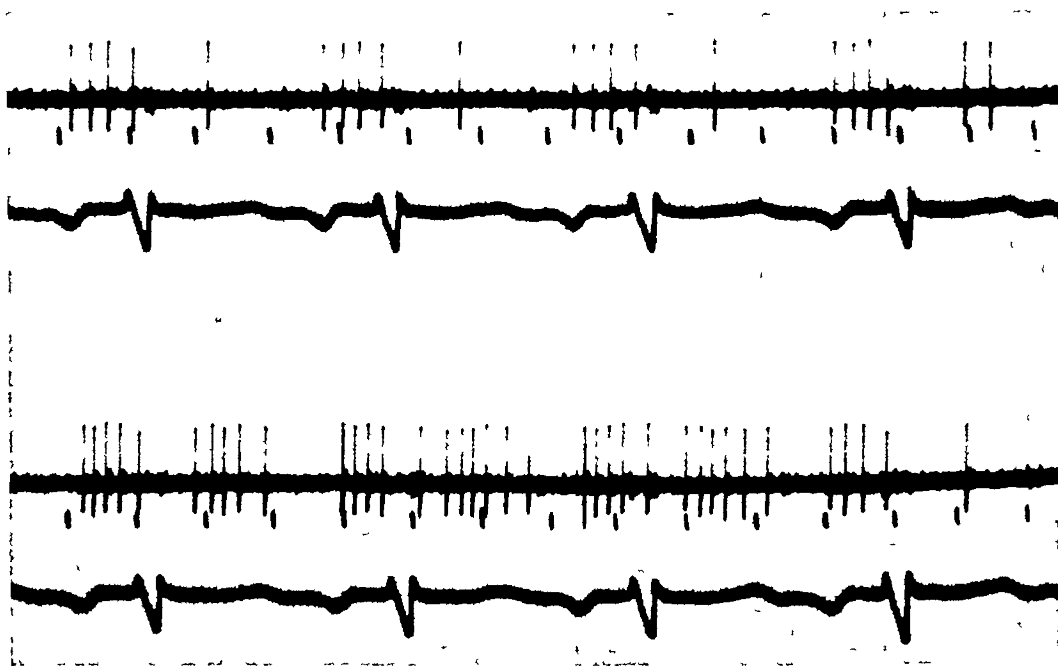


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Dawes· They are almost certainly atrial receptors These are very characteristic

Burch Did the heart stop?

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Heymans Dr Dawes, are these action potentials related to fibers

to the coronary chemoreflex He made the very provocative and interesting suggestion that there might be stretch receptors in the walls of the ventricles Perhaps I should say that he repeated the suggestion originally made by von Bezold and Hirt (34) in 1867, that there were sensory receptors in the walls of the ventricles which, when excited, would cause a fall in blood pressure and heart rate, and that this might re-enforce the aortic depressor reflex It is a very attractive idea It has been called a cardio-circulatory reflex. a reflex originating from the heart itself, which regulates the circulation

Heymans Dr Dawes, do you not believe that in the heart, at least on the left side, the presso-receptors of the aortic arch may go to the atrium and ventricle? It has been shown, I think by de Castro and Nonidez, that there are presso-receptors in the left side of the heart which belong to the same structure as the aortic arch presso-receptors That is why I always speak of cardio-aortic presso-receptors Daly and Verney (1,35) showed that these left heart receptors respond to pressure variations Afferents also arise from the roots of the superior and inferior venae cavae and pulmonary veins, and perhaps from the right atrium Nonidez showed that the receptors of these afferents have the typical structure of presso-receptors

Dawes In general, I would agree with you, but I think that these types of receptors, and their afferent parts, require a great deal of further study before we can be certain In this particular instance, certain difficulties stand in the way of concluding that the afferent pathway of the Daly and Verney reflex is that of the aortic depressor fibers The reason I am not convinced of this is as follows the aortic depressor nerves can be seen in the dog entering the arch of the aorta and running down it In Daly and Verney's experiment, they cut a hole part of the way through the ascending aorta immediately above the coronary orifice They inserted a cannula, and then tied a ligature around the ascending aorta I cannot believe that any nerve fibers running down the ascending aorta toward say, the orifices of the coronary arteries or the aortic ring, could have preserved their integrity under those conditions

Heymans I absolutely agree with your statement that the afferent pathways require more study We know something about the localization of receptors from observing presso-receptors, but the pathways of the different fibers coming from this area have to be investigated, and a number of them are yet to be found However, as you have already said, in the vagus nerve there are many afferent

Burch. In the electrocardiogram, the peak of the P wave occurred at just about the same time as the discharge began?

Dawes. Yes

Burch The pressure within the atrium might have occurred a little later Did you have any pressure recordings?

Dawes. In one or two dogs we used a left atrial condenser manometer at the same time. We assured ourselves that the frequency of discharge of these atrial receptors was related pretty closely to the pressure, the experiments were complicated without the condenser manometer, and this was just one more instrument to look after

Selkurt. If you artificially elevated the pressure within the atrium, would you obtain an enhanced discharge?

Dawes. Yes If saline is injected intravenously an increase in the frequency of discharge is obtained in these fibers The work of Whitteridge and his colleagues (8,9,10,31,32) indicates that these must have been atrial receptors

THE DALY AND VERNEY REFLEX

I should like to discuss reflex Number 3 in Table IV, the coronary chemoreflex, and its separate identity from Number 4, which refers to the work of Daly and Verney (1) They inserted a cannula, pointing toward the heart, into the ascending aorta within a few millimeters of the coronary orifice, and they raised the pressure in this cannula, thereby increasing the pressure in the left ventricle and the coronary artery. They observed a slowing of the heart Their preparation was such that they could not see whether there was peripheral vasodilation or a change in respiration They found that slowing of the heart was abolished by cutting the vagi

They also put a nondistensible bag around both ventricles, and sealed around the atrio-ventricular junctions to reduce the pressure inside this bag They again showed that this caused bradycardia, which was abolished by cutting the vagi

Fremont-Smith When you say they "reduced the pressure," do you mean subatmospheric?

Dawes They reduced the outside pressure, thereby increasing the relative pressure across the ventricular walls They concluded, from these observations, that there was a reflex, but not the aortic depressor reflex, which originated from somewhere inside the ventricles

I think it is a very important observation, and the experiment should be repeated It is the only clue we have to substantiate the idea which Jarisch (33) put forward when he drew our attention

Richter (33) did that experiment in 1939 They put procaine into the pericardial sac and abolished the reflex I think one has to be a little cautious about drawing conclusions about the anatomical distribution of the receptors or their afferent nerves from such studies, because we know that the reflexes are very sensitive to the intravenous administration of procaine, or other local anesthetics, and these substances are rapidly absorbed

Burton Do you think the sensory receptors for the coronary chemoreflexes are implicated in the cardiac afferent discharges after coronary occlusion? In a great many experiments on dogs, if the heart is deafferented the immediate deaths are very much modified, although the final deaths are not I was wondering if you have ever tried to find out whether these receptors fire off upon coronary occlusion

Dawes I think it is a possibility, but experimental evidence is lacking We have tried tying off a main coronary artery in a dog, and I could never convince myself that this procedure caused the coronary chemoreflex However, there are so many other factors which enter in when you tie a main coronary artery in an animal, that I think the experiments were inconclusive

Heymans Fleckenstein (36) showed that intravenous injection of procaine also holds out the receptors of the so-called Bezold-Jarisch reflex

Dawes That is the coronary chemoreflex

Heymans Yes That was also true according to some clinical observations However, I think we have to be careful about assuming that, in the patient with a coronary infarct and with the low blood pressure occurring after it, intravenous injection of procaine is effective We can only speculate on the possibility that, because the reactions in experimental clinical observations are similar, hypotension in coronary infarct may be related in some way to this special group of receptors However, I do not think there is enough evidence to draw the conclusion that in coronary occlusion the blood pressure gets low, because these sensory coronary chemoreceptors are really stimulated

Comroe There are two substances sometimes present in coronary occlusion, which might be found locally in sufficient concentration to stimulate coronary chemoreflexes One, of course, is 5-hydroxytryptamine, which may appear in high concentration whenever blood clots and platelets disintegrate, the other is adenosine triphosphate, which is in close relation to these sensory receptors whenever tissue disintegrates

fibers If, in a dog, the depressor nerve is cut high up in the neck between the sympathetic and the vagus, depressor fibers and other afferents may still be left in the vagus nerve

Nickerson Our knowledge of all these reflexes starts out with observations on a more or less localized area We are then faced with the question of how far we can group these into a monistic concept of activity We need some definition of the criteria we are going to use for this grouping One that has been discussed relates to the nervous pathways involved Here we run into difficulty, because everything depends upon where we draw the line in deciding whether the same nervous pathways are involved If we go far enough up the vagus, they obviously are running in the same nerve If we go down to the receptors, each is probably running in a different nerve

Another possible criterion, which I think involves similar difficulties, relates to the histological characteristics of the receptor areas themselves If we follow this rigorously, we would not distinguish between the aortic and the carotid receptors, yet because of the elongation of the neck during development, they are nicely separated. My own feeling is that perhaps we had best consider these responses separately until we have more than one criterion for combining them

Alexander Reference has been made to the deafferentation which results from passing a ligature around the ascending aorta In respect to the receptors you have described in the ventricles, is there any information as to how likely one is to deafferent the preparation by tying a cannula into a coronary artery? Do the afferent fibers run close enough to the coronary vessels to be caught by the ligature?

Dawes Apparently not I have often tied ligatures around different branches, such as the left circumflex, the anterior descending, or smaller branches of those arteries, and also around the main left circumflex artery itself at its origin from the aorta The coronary chemoreflex has remained intact

Comroe However, you do know about pressure reflexes?

Dawes I do not know about the Daly and Verney reflex The other point is that I have tried to abolish the reflex by destroying the nerves in the atrioventricular grooves, and I have obtained only equivocal results, sometimes successful, but usually not

Moe Will a local anesthetic injected into the pericardial space block this coronary chemoreflex?

Dawes I have not done experiments of that type Jarisch and

observation that procaine blocks the so-called Bezold reflex However, it is necessary to use doses of the order of from 10 to 15 mg per kg, and at that level of dosage it can readily be demonstrated that the vagal ganglion has been blocked

Dawes. It may well be so, it is just one of these points that will have to be borne in mind

Richardson. We also observed that although intravenous procaine blocked the cardiovascular part of the reflex, there was no effect upon the respiratory reflex, which suggests that procaine blocks only the efferent pathways of the reflex

PULMONARY DEPRESSOR REFLEXES

Dawes I suggest we proceed to reflexes Number 5 and 6 in Table IV (p 45) I should like to review the evidence for the existence of the pulmonary depressor reflex and the pulmonary depressor chemoreflex By the pulmonary depressor reflex, I mean the reflex fall in blood pressure and heart rate which is observed on raising the pressure in the pulmonary circulation

There are at least six groups of workers who have investigated this phenomenon beginning, in 1929, with Churchill and Cope (40) experiments were continued by Schwiegk (41), Schweitzer (42), Daly, Ludany, Todd and Verney (43), Parin (44) and, more recently, Aviado and his colleagues (4)

Briefly, what they have done is as follows Schwiegk, Schweitzer, and Parin tied a cannula into the left pulmonary artery in dogs and cats, and raised the pressure in the left lung, usually, but not always, with occlusion of the pulmonary veins, and they found a small fall in blood pressure and heart rate Daly and his colleagues, and Aviado, *et al*, used rather complicated perfusion systems in which the left lung was perfused from the left pulmonary artery, and the blood flowed out from the left pulmonary veins The left atrium was therefore excluded They also found a fall in blood pressure and heart rate on raising the pressure in the left lung They had the impression that the reflex might be coming from sensory receptors on the venous side, because the reflex was more readily obtained on obstruction of venous outflow than on raising arterial pressure

The interesting thing to me about this reflex is that it is very difficult to obtain I think everyone who has worked with it agrees it can only be observed in a certain number of animals, by the use of large pressures in most experiments – I should say unphysiological pressures – and the response is very slight On the other hand, it is undoubtedly true that the effect is abolished by cutting the vagi

The unfortunate part about this theory is that while 5-hydroxytryptamine, injected into the coronary artery in the cat, will produce a fall in blood pressure reflexly by way of the vagus nerve, it does not seem to do so in dogs. It is also unlikely, from what little evidence there is, that it does so in man.

One more point ought to be mentioned, and that is that in man, intravenous injection of 5-hydroxytryptamine, and adenosine triphosphate, both produce symptoms which in certain respects stimulate those of coronary occlusion, i.e., substernal oppression. It may well be that they stimulate some sensory receptors in this area which are also stimulated by mechanisms involved in coronary occlusion. However, this is pure theory.

Nickerson: Agress, Clark and the group (37) in California, have worked on the production of shock from coronary occlusion. As we have known for a long time, the tying of a coronary artery, even though it will kill an animal, does not result in prolonged hypotension. These workers found they could produce the state of shock, which is seen in a certain percentage of patients with coronary occlusion, by embolizing the coronary vessels with spheres of, I believe, about 300 microns, which seem always to lodge at a particular bifurcation in the coronary vessels. Spheres of larger diameter, although they produce equal damage, do not produce this picture of shock. This may give us some clue as to the localization of the neurogenic afferents involved.

Comroe: Unfortunately, they did not repeat this after the vagus nerves had been blocked, so there is no proof that it is a reflex.

Nickerson: No, there is a great deal of work yet to be done.

Shorr: Would this hold for the breakdown of adenosine triphosphate? I ask that because one could not conclude that these high-energy phosphates would remain in the triphosphate stage in an anoxic muscle.

Comroe: I think that adenosine itself, or certain adenosine compounds, will produce a marked hypotension. The group at Sloan-Kettering have shown that (38). We obtained a very small amount of their most active material, 2-chloroadenosine, and confirmed that it produces a hypotension, but we did not have enough to do localization studies to ascertain whether the hypotension was really reflex, or whether it resulted from direct peripheral dilation.

Dawes: Emmelin and Feldberg (39) did some work on adenosine triphosphate, and their paper may have further information about whether other breakdown compounds are likely to be active.

Richardson: We have been able to confirm Fleckenstein's (36)

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Nickerson: Agress, Clark and the group (37) in California, have worked on the production of shock from coronary occlusion. As we have known for a long time, the tying of a coronary artery, even though it will kill an animal, does not result in prolonged hypotension. These workers found they could produce the state of shock, which is seen in a certain percentage of patients with coronary occlusion, by embolizing the coronary vessels with spheres of, I believe, about 300 microns, which seem always to lodge at a particular bifurcation in the coronary vessels. Spheres of larger diameter, although they produce equal damage, do not produce this picture of shock. This may give us some clue as to the localization of the neurogenic afferents involved.

Comroe: Unfortunately, they did not repeat this after the vagus nerves had been blocked, so there is no proof that it is a reflex.

Nickerson: No, there is a great deal of work yet to be done.

Shorr: Would this hold for the breakdown of adenosine triphosphate? I ask that because one could not conclude that these high-energy phosphates would remain in the triphosphate stage in an anoxic muscle.

Comroe: I think that adenosine itself, or certain adenosine compounds, will produce a marked hypotension. The group at Sloan-Kettering have shown that (38). We obtained a very small amount of their most active material, 2-chloroadenosine, and confirmed that it produces a hypotension, but we did not have enough to do localization studies to ascertain whether the hypotension was really reflex, or whether it resulted from direct peripheral dilation.

Dawes: Emmelin and Feldberg (39) did some work on adenosine triphosphate, and their paper may have further information about whether other breakdown compounds are likely to be active.

Richardson: We have been able to confirm Fleckenstein's (36)

observation that procaine blocks the so-called Bezold reflex However it is necessary to use doses of the order of from 10 to 15 mg per kg and at that level of dosage it can readily be demonstrated that the vagal ganglion has been blocked

Dawes It may well be so it is just one of these points that will have to be borne in mind

Richardson We also observed that although intravenous procaine blocked the cardiovascular part of the reflex there was no effect upon the respiratory reflex which suggests that procaine blocks only the efferent pathways of the reflex

PULMONARY DEPRESSOR REFLEXES

Dawes I suggest we proceed to reflexes Number 5 and 6 in Table IV (p 45) I should like to review the evidence for the existence of the pulmonary depressor reflex and the pulmonary depressor chemoreflex By the pulmonary depressor reflex, I mean the reflex fall in blood pressure and heart rate which is observed on raising the pressure in the pulmonary circulation

There are at least six groups of workers who have investigated this phenomenon beginning in 1929 with Churchill and Cope (40) experiments were continued by Schwiegk (41) Schweitzer (42) Daly Ludany Todd and Verney (43) Parin (44) and more recently Aviado and his colleagues (4)

Briefly what they have done is as follows Schwiegk Schweitzer and Parin tied a cannula into the left pulmonary artery in dogs and cats and raised the pressure in the left lung usually but not always with occlusion of the pulmonary veins and they found a small fall in blood pressure and heart rate Daly and his colleagues and Aviado *et al* used rather complicated perfusion systems in which the left lung was perfused from the left pulmonary artery and the blood flowed out from the left pulmonary veins The left atrium was therefore excluded They also found a fall in blood pressure and heart rate on raising the pressure in the left lung They had the impression that the reflex might be coming from sensory receptors on the venous side because the reflex was more readily obtained on obstruction of venous outflow than on raising arterial pressure

The interesting thing to me about this reflex is that it is very difficult to obtain I think everyone who has worked with it agrees it can only be observed in a certain number of animals by the use of large pressures in most experiments — I should say unphysiological pressures — and the response is very slight On the other hand it is undoubtedly true that the effect is abolished by cutting the vagi

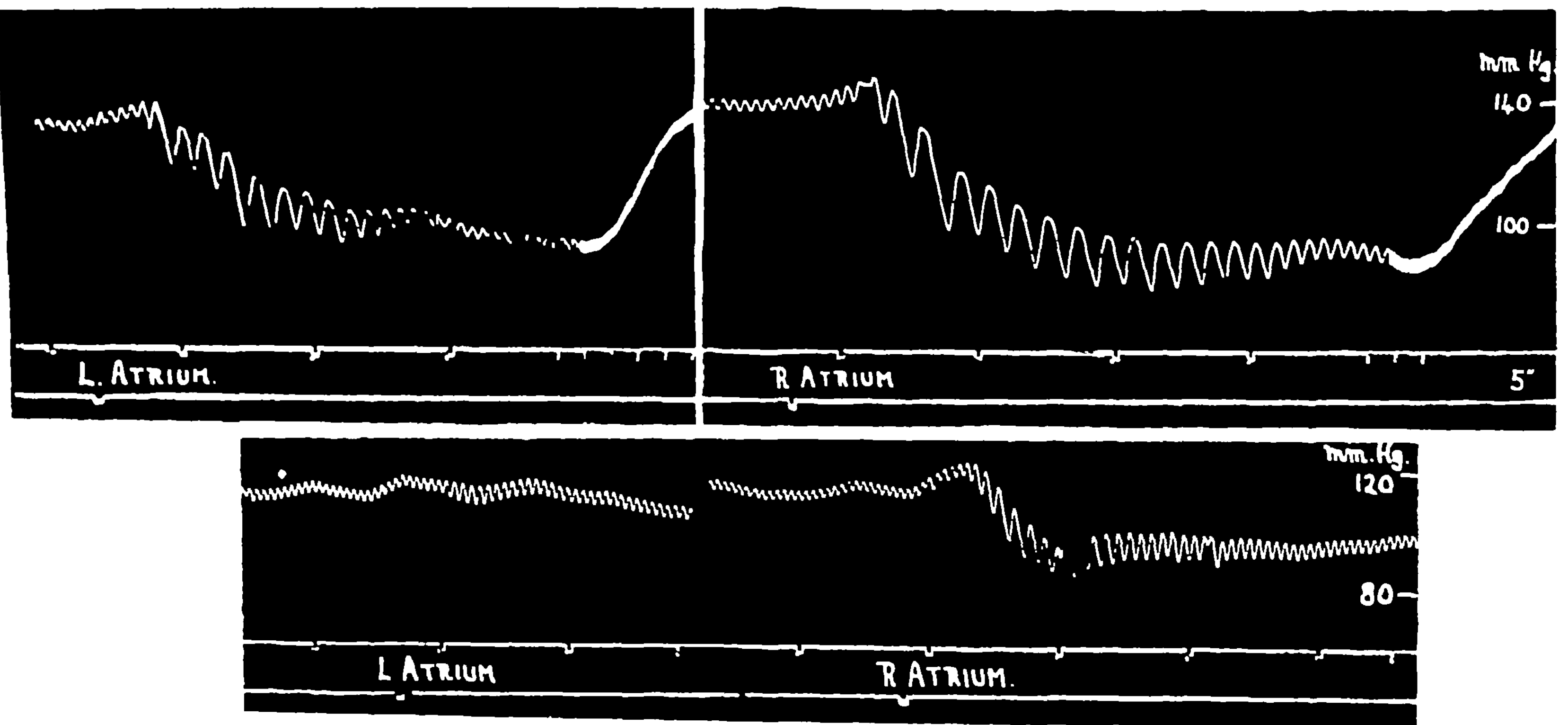


Figure 21 Cat, chloralose anesthesia, chest opened in midline, artificial ventilation, cannulae for injection tied into both atrial appendages Record of blood pressure At each signal 100 µg phenyl diguanide was injected into the atria as indicated Between the upper and lower parts of the tracing all accessible nerve fibers running in the atrio-ventricular grooves were divided Reprinted, by permission, from Dawes, G S, and Mott, J C Circulatory and respiratory reflexes caused by aromatic guanidines *Brit J Pharmacol* 5, 65 (1950)

argument of assessing site of action by magnitude of response If a drug circulates through the body before it reaches the site of action there are many possible factors which could alter the magnitude of the response obtained and I am wondering whether the latency is not more important

Dawes I think both are necessary are they not?

Alexander Except that the latency seems to me much less subject to error The magnitude of the response can be altered by so many factors

Dawes But you would not disagree with the general conclusion

Moe Dr Dawes are you proposing that the response obtained on injection into the left atrium is from the coronary chemoreflex?

Dawes Yes

Alexander In a situation such as this suppose that a drug were acting on the cardiovascular centers in the brain stem Suppose also that there were an enzyme in the lung which could alter the drug to increase its activity The drug injected into the right atrium so that it circulated through the lungs first would be more effective than that which went directly to the centers It seems to me that there are so many possibilities of this type that latency becomes the real key to localization

Dawes I agree with you that I would put more emphasis on *latency than on magnitude of response* but I think *magnitude* of the response is quite striking and that you have to have that also

Figure 22 shows another method of differentiation and that is by cooling the vagi It illustrates the fact that cooling the vagi to 8 C will block the coronary chemoreflex but not the pulmonary chemoreflex *A B* and *C* are injections of veratridine At *C* when the vagi were at room temperature a fall in blood pressure and in heart rate was obtained When the vagi were cooled to 10 C for two minutes before the injection of the drug there was still a fall in blood pressure and in heart rate However when the vagi were cooled to 8 C the fall in blood pressure and heart rate was abolished. Contrast this with injections not of phenyl diguanide but *of 2 a naphthyl ethyl isothiourea, another amidine derivative* and you see that the responses are of the same size both as to blood pressure and heart rate whether the vagi are cooled to 8 C or to room temperature That is another distinction between the coronary chemoreflex and the pulmonary depressor chemoreflex

Comroe Dr *Dawes is that* a general distinction *or is it* one which applies only to the drug veratridine? Are there other chemi

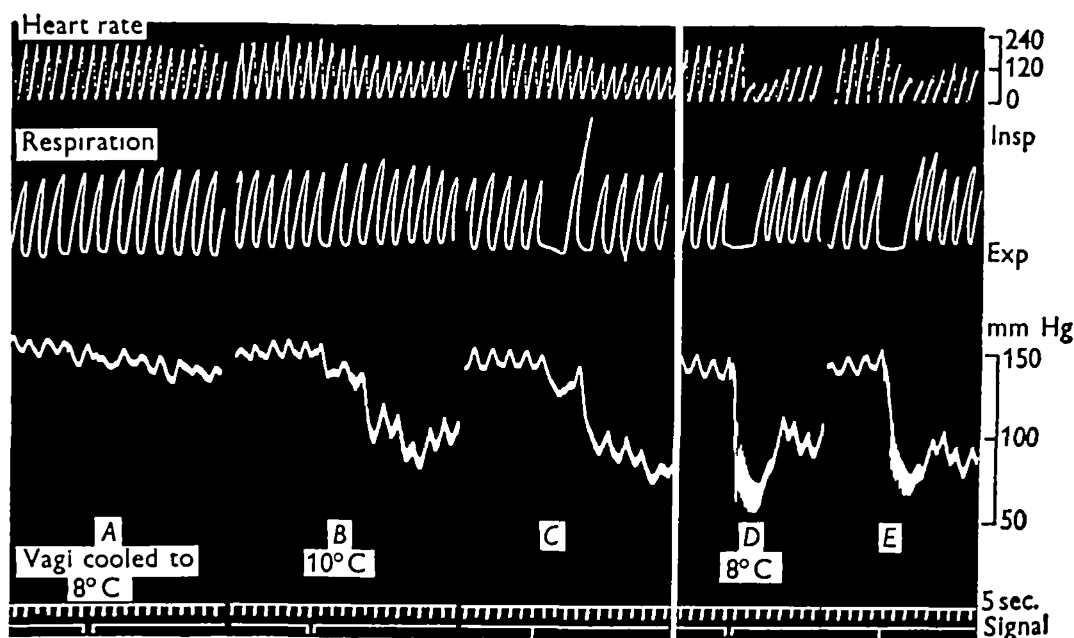


FIGURE 22 Cat, chloralose anesthesia Records of heart rate (beats per minute as in Figure 8) of respiratory movement from a body plethysmograph, and of carotid arterial blood pressure Injections of 20 μg veratridine at *A*, *B* and *C*, and of 100 μg 2 α-naphthyl ethyl isothiourea at *D* and *E* The cervical vagi were cooled for 2 minutes to 8°C at *A* and *D*, and to 10°C at *B* Reprinted, by permission, from Dawes, G S, Mott, J C, and Widdicombe, J G Respiratory and cardiovascular reflexes from the heart and lungs *J Physiol* **115**, *258 (1951)* Cambridge Univ Press

cals which can act at both sites blocked in a different fashion by cooling?

Dawes The only drug which I think we have information on is veriloid, which is a mixture of veratrum alkaloids Veriloid, slowly infused into a cat, causes a fall in blood pressure and heart rate by the coronary chemoreflex, and that also is blocked by cooling the vagi to 8° C So far as other drugs are concerned, I do not think that a thorough analysis has been made of the phenomenon

Moe What about adenosine triphosphate?

Dawes So far as I know, it has not been analyzed in this fashion Although I have presented this picture from the point of view of the amidine derivatives, they were by no means the first substances which were shown to have this effect As along ago as 1900, Brodie and Russell (45) investigated a similar phenomenon with serum in cats, and in 1942, Bagoury and Samaan (46) did a very beautiful analysis of the effect of acetoacetate in dogs It is curious, I think, that more attention has not been paid in the past to these substances I have concentrated on the analysis of the amidines because I personally happen to know more about them than either serum,

adenosine triphosphate serotonin acetoacetate or the many other substances which are supposed to produce these effects

Richardson Dr Dawes in your experience is it true that the dosage response curve of this particular kind of phenomena is extremely steep that is if one gradually increases the dose of a reflex inducing agent one reaches a point where the reflex is suddenly induced although a slightly lower dose is without effect It is almost like an all-or none response

Dawes That has been true with phenyl diguanide

Moe It is also true with protoveratrine and veratridine

Heymans Dr Dawes you raise two interesting points First I quite agree that it is not easy to obtain blood pressure responses by changing the pressure in the pulmonary circulation and if something happens in the systemic circulation responses to changes in the pulmonary arterial pressure are always very slight and also difficult to repeat in the same animal Second if there is a positive response produced by changing the pressure in the pulmonary arterial system we do not know where that response is coming from it may be from the pulmonary artery or from the venous side

As you say there is a third difficulty namely that in order to create favorable conditions for the response we have to increase intrapulmonary arterial pressure to a very high level and then we do not know whether we are interfering with the pulmonary stretch receptors which also are affecting reflexly the heart rate and so the blood pressure In your opinion is there a possibility that drugs injected into the pulmonary circulation acting on some chemo receptors or stretch receptors in the lungs and affecting the threshold of these stretch receptors would condition reflexly the heart rate?

Dawes So far as the pulmonary stretch receptors the classical stretch receptors of Adrian are concerned the first point is that neither phenyl diguanide nor 2 α naphthyl ethyl isothiourea affects their activity at all as measured by single fiber records Secondly the pulmonary stretch receptors are entirely blocked by cooling the vagi to 10 C Yet the amidine derivatives phenyl diguanide and so on retain their characteristic activity when the vagi are cooled to 10 C Thirdly I do not believe that the pulmonary stretch receptors affect the cardiovascular system because the vagi may be cooled to 10 C without evidence of any change in the circulation. Moreover a small intravenous injection of veratridine which sensitizes the pulmonary stretch receptors will cause them to fire continuously but the bradycardia and the fall of blood

pressure come on after such a long latency that the veratridine, by then, must have reached the coronary chemoreflex receptors In fact there is no evidence, of a change in the cardiovascular system due to sensitization of the pulmonary stretch receptors

So far as the other types of sensory receptors in the cardiovascular system are concerned, the aortic presso-receptors are blocked by cooling to about 8° C, as Whitteridge (9) showed The atrial receptors, types A and B, are also not sensitized or excited by phenyl diguanide, or 2 α-naphthyl ethyl isothiourea

Two other types of receptors which have come to our attention recently, pulmonary arterial and mediastinal, have not been investigated adequately There are some observations by Widdicombe on the mediastinal receptors, and I think it is likely that they also will be blocked (I am not quite sure about this point), by cooling to 8° or 10° C They are quite large fibers

We have no electrophysiological evidence of the types of fibers which are excited by the amidine derivatives No attempts have been made, so far as I know, to study the effects of serotonin, acetoacetate, or other types of drugs on sensory nerve fibers in the vagus The probability is that the fibers involved are small ones, because the observations of Whitteridge and his colleague, Paintal, strongly suggest that the larger fibers, which have a higher conduction velocity and a larger diameter, are blocked by cooling to temperatures greater than those at which small fibers are blocked (8) Thus, I think it is likely that the afferent fibers for the pulmonary depressor reflex are probably small ones That would explain why they are so difficult to find

Howard Dr Dawes, in regard to Number 5, in Table IV (p 45), which is the pulmonary depressor reflex, might a patient with pulmonary stenosis before and after aortic pulmonary anastomosis, prove a useful subject to study?

Dawes I do not know

Moe Are you thinking of congenital pulmonary stenosis, close to the right ventricle?

Howard Yes

Moe I do not think you would be exciting these receptors in that case, would you?

Dawes I should doubt it

Nickerson They might be excited after the operation

Liljestrand It is known that if an animal is given, say, 50 per cent oxygen instead of air, there is a decrease in the resistance within the pulmonary vascular bed, which seems to be due to some

local mechanism This has been proved not only in cats but also in dogs and man

In answer to Dr Howard's question I think if the circulation is improved through the lung it is to be expected that the pulmonary pressure will go down just as happens during oxygen breathing in normal man and in animals

Burton I do not think we should neglect to mention the pulmonary reflex which was described so ably by Smith (47) in 1948 He produced an embolus in the pulmonary system by injecting colloidal material into a very small distributing artery so that it entered a very tiny lobule of the lung In a very dramatic way the pulmonary arterial pressure rose within two minutes to very high values This was followed by a fall of the arterial pressure and the animal was dead That was a picture of clinical pulmonary embolism This result was not abolished by cutting the vagi the only way he could do so was to cut the main artery supplying that lobe of the lung in which he had caused the infarct place a plastic or glass tube in between and cut right around the wall of the artery He could then infarct this area quite extensively and nothing happened whereas if the artery were intact the entire lung vasculature went into spasm

I think this is a very interesting reflex because at first sight this seems only deleterious to an animal but then one might indulge in teleology and speculate that perhaps there are "near infarcts" that are likely to occur all the time This reflex or spasm raises the pressure in the pulmonary system and perhaps blows out the obstruction Unfortunately it does not always blow them out and the animal dies in a crisis Without this reflex his pulmonary function would be affected very little

Comroe Unless great care is taken by means of an obstructing cuff around the catheter the injections of emboli are not localized They go forward until they impact and then backward and spread throughout both lungs This I believe is now recognized by Smith and Hara (48) and also Haynes (49) who several years ago reported similar experiments in abstract form When others have attempted to do this same experiment by injecting embolic materials through a catheter distal to an obstructing cuff these dramatic results have not been obtained.

Carlens (50) in Sweden and several groups in this country have passed cuffed catheters into the right or left pulmonary artery of unanesthetized man and have inflated a balloon near the tip of that catheter to such an extent that blood flow through that particular

lung was completely shut off I assume that the pulmonary artery around the inflating balloon must have been put under a fair amount of stretch Yet there was no discomfort and there were no appreciable effects on systemic or arterial blood pressure Thus a reflex, at least of catastrophic nature, does not appear to arise in unanesthetized man from the stretch of the main pulmonary arteries I do not think there is yet definite proof that it does or does not originate from smaller branches of the pulmonary arteries

Kinsely It may be of interest that Irwin and Burrage (51), of the Massachusetts General Hospital, have just observed that on the second injection of an allergin into sensitive animals, there is a complete contraction of pulmonary arteries, capillaries, and veins They have recorded these contractions in motion pictures Thus, these pulmonary vessels, at least in some species, can contract with great power

Dawes I think it would be instructive to discuss how these amidines might work It is not due to spasm of the pulmonary arteries If they are injected into an animal with its vagi cut, we do not see any change in pulmonary arterial pressure Therefore, it is not a direct effect on the vessel walls, at least, not on the large vessel walls

There are some other possibilities In dogs, it would appear that phenyl diguanide can excite the chemoreceptors of the aortic and carotid bodies Thus, this drug has the potentiality of exciting some kinds of chemoreceptors

Paintal (8,31,32), working on cats in Whitteridge's laboratory, found that there were some small vagal afferent sensory fibers which did not have any spontaneous activity They did not have a cardiac or a respiratory rhythm, but they were excited by intravenous injection of phenyl diguanide, and it seemed at first that this might explain some of the phenomena However, recently, after his return to India, he found that these fibers originated in the stomach, and he believes that there are stretch receptors there which are excited by phenyl diguanide in some way or other (having circulated, that is, through the heart and lungs, and eventually having reached the stomach) There is a possibility that these substances may excite chemoreceptors, or stretch receptors We have no evidence to tell us what they are doing in the lungs, and I think we will just have to leave that question open

Heymans I have some data (52) on the aortic and carotid chemoreceptors not being stimulated by phenyl diguanide In our experiments on dogs, we looked for this, and found that the chemo-

receptors of the aortic and carotid bodies did not respond to this drug. Our conclusion was that the site of action is mainly in the heart and lungs without being able to localize exactly the place of action. What is your opinion, Dr. Dawes?

Dawes: I should like to make it clear that the difference of opinion between Dr. Heymans and myself relates to the effect of phenyl diguanide in dogs as opposed to its action in cats. In the latter it causes a fall of blood pressure and heart rate which is abolished by cutting the vagi. In dogs it causes bradycardia, a rise of blood pressure, and respiratory stimulation.

Dr. Heymans showed that the latency between intravenous injection and the onset of the bradycardia and the respiratory stimulation was quite long, from about seven to ten seconds. We made the same observation. On that basis we were prepared to conclude that the receptors were not in the lungs.

Fremont-Smith: Would you specify the exact difference in the results that you and Dr. Heymans have obtained? When one has the good luck to find two investigators who appear to have done the same experiment and obtained different results, then one has an opportunity for a really instructive development, because obviously something is wrong. Apparently they did not do the same experiment. Rather than saying "I could not confirm your results," it might be better to say "Why didn't I do your experiment? Was it either because you didn't describe it well enough for me to repeat it, or did I have a bright idea of a short cut, or a different technique, which meant that I actually did a different experiment. Was it because I used a young dog and you used an old one, was it the anesthesia, or the sex of the dog?"

Dawes: I think the difference is probably mainly one of interpretation.

Richardson: There is no disagreement as to the actual response in dogs. You both obtained stimulation of respiration.

Dawes: Yes, we both agree on that.

Heymans: The difference is that Dr. Dawes claims phenyl diguanide in dogs induces the responses by stimulation of the chemoreceptors in the carotid and aortic bodies, and I have not been able to obtain that stimulation.

Dawes: Perhaps I could describe the difference in experimental conditions. Figure 23 illustrates an experiment performed with a preparation from the carotid body nerves which contained two fibers (lower record). The upper record is of arterial blood pressure. There are two types of fibers, a large fiber which fires every time

the heart beats, and a small fiber which fires continuously Sometimes the two fibers fire at the same time, and when they do one obtains a potential which is the sum of the two That is the explanation for these occasionally slightly larger potentials

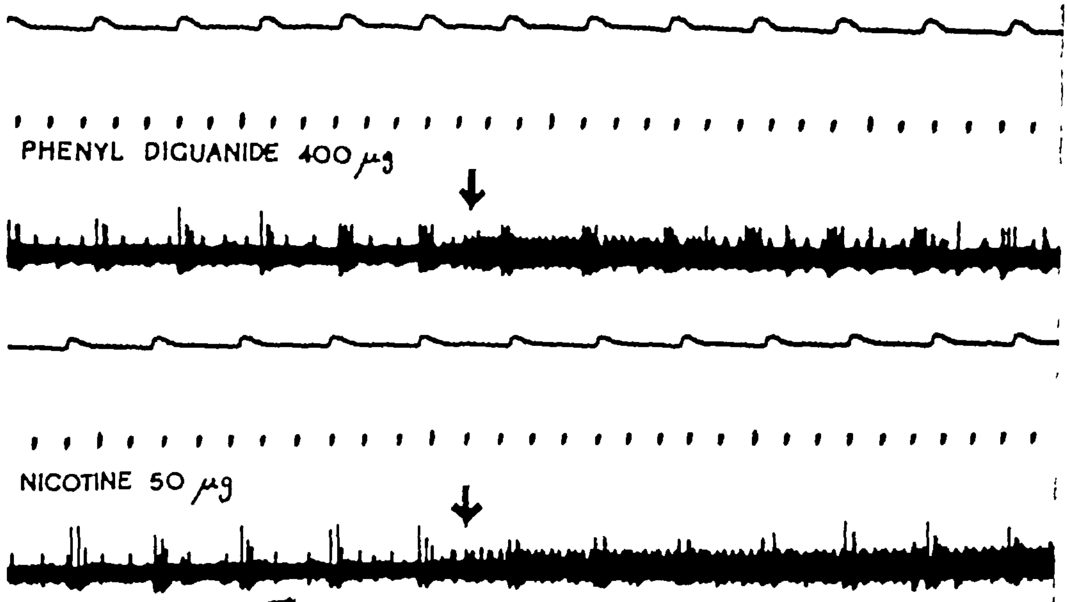


FIGURE 23 Dog, chloralose anesthesia Systemic arterial blood pressure held constant by stabilizer in abdominal aorta Records of blood pressure from R brachial artery by a condenser manometer (above), time in 1/10 seconds, and of action potentials recorded from a small part of the R carotid sinus body nerve The upper record shows the response (beginning at the arrow) to the injection of 400 μg phenyl diguanide into the right superior thyroid artery, and the lower record to 50 μg nicotine The larger fiber, which has a cardiac rhythm, is characteristic of a presso-receptor, the smaller fiber, which responds to both phenyl diguanide and nicotine, is presumed to come from a chemoreceptor Reprinted, by permission, from Dawes, G S, Mott, J C, and Widdicombe, J G Chemoreceptor reflexes in the dog and the action of phenyl diguanide *Arch internat pharmacodyn* **90**, *203 (1952)*

Heymans These fibers are connected with presso-receptors and chemoreceptors?

Dawes I think the larger fiber is definitely from a presso-receptor, and the smaller from a chemoreceptor As shown in the upper section of Figure 23, we injected 400 μg of phenyl diguanide into the carotid artery through the right superior thyroid artery (53) As a result the chemoreceptor fiber began to discharge continuously Below, we injected 50 μg of nicotine, and again the chemoreceptor fiber fired continuously in response It was the same fiber and the same preparation

Acheson What is the time scale on this record? It looks like a very short latency

Dawes The arrows do not indicate the time of injection but when the response began The time of injection was a few seconds earlier

Acheson May I then call attention to the difference in the experiments? You Dr Dawes demonstrated an effect on a receptor via a single nerve fiber whose function you were not able to assign You Dr Heymans got the reflex

Dawes We also used the catheter technique which Dr Comroe used to localize the site of action to the aortic body We found that when a catheter was passed down the left common carotid artery so that it lay in the arch of the aorta or the ascending aorta and when the drug was injected through that catheter the stimulation of respiration and the rise of blood pressure would be obtained When we withdrew the catheter slightly the response disappeared That was the basis for our conclusion that it was an action on the aortic body

Heymans As Dr Fremont Smith suggested there may perhaps be some other reason why we did not get the same results perhaps because we used a different technique Perhaps too it is because our animals were in a different condition from yours May I ask what anesthesia was used?

Dawes We used chloralose and pentobarbital I think

Heymans In our experiments we used only chloralosane which is a pure parachloralose because we know it is less toxic and interferes less with responses

Fremont Smith It is quite possible that this would cause a difference in result.

Heymans I do not feel that is the only difference because we also used different experimental methods

Dawes I have not done perfusion experiments as you have

Fremont Smith There is a point I should like to make The cerebrospinal fluid pressure is elevated by histamine if one uses ether as the anesthesia but if one is using a barbiturate the cerebrospinal fluid pressure is lowered by injection of histamine This is a diametrically opposite result Thus the question of anesthesia is by no means to be ignored.

Richardson Dr Heymans when you denervate the carotid sinus does phenyl diguanide produce stimulation when it is injected intravenously?

Heymans Doing what Dr Dawes did that is denervating both

the heart beats, and a small fiber which fires continuously Sometimes the two fibers fire at the same time, and when they do one obtains a potential which is the sum of the two That is the explanation for these occasionally slightly larger potentials

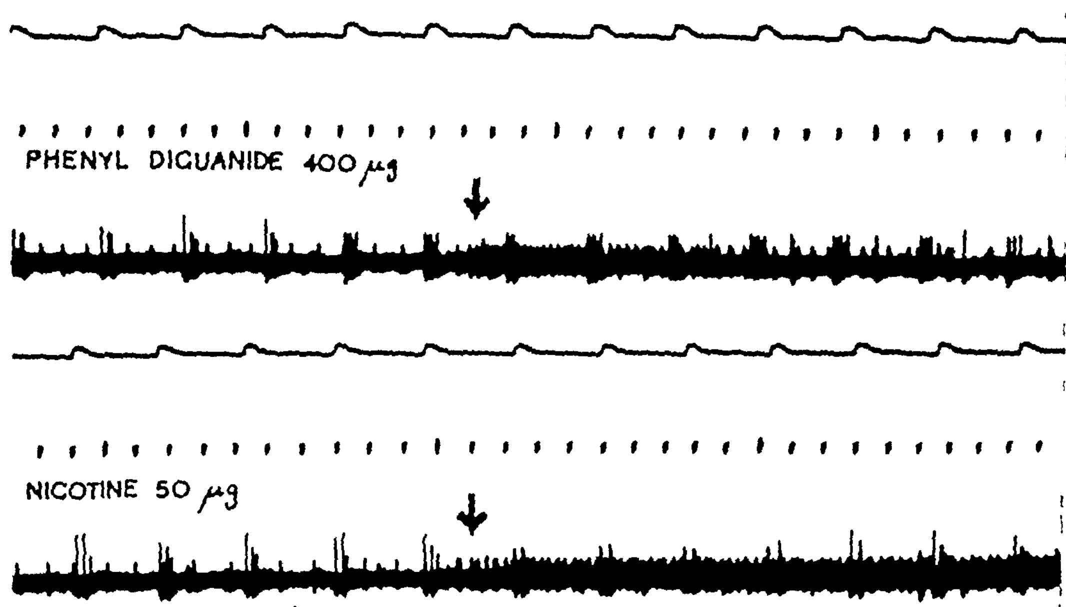


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know we obtain a diuresis How is this caused? It might be due to some reflex and if so where would the reflex come from? Possibly from the venous system or the right atrium The evidence for this being a vagal reflex is not very good as yet but it is one possibility

These are the four hypotheses for the central action of atrial receptors I should like to point out one very peculiar feature of the second that is the reflex suggested by Aviado *et al* (4) If a drug is injected which causes a reflex bradycardia this results in a rise in atrial pressure both on the left and right sides of the heart If phenyl diguanide or veratridine is injected a large fall of blood pressure and heart rate is first observed and this is followed by a rise of left and right atrial pressure If this second hypothetical reflex exists by which an increase in the right or left atrial pressure would cause a fall of blood pressure and heart rate this would constitute a positive feedback mechanism This would increase even further the depressor effect and the bradycardia I put this idea forward just for discussion It certainly would be difficult to fit in with our current ideas of the circulation being a homeostatic mechanism. On the other hand we know that there are some phenomena such as fainting which are very difficult to explain

I should be very much interested in hearing what you think about these various hypotheses What are the purposes of these atrial receptors are they important in homeostasis? Do they alter it? Do they shift the volume of blood from the lungs to the periphery? That is one possible explanation of their function

Heymans Again however we face the same difficulties mainly because the action potentials do not seem to run in the same direction as the classical Bainbridge reflex Some other experiments also seem to contradict the observations of Bainbridge I believe these contradictions could be settled only by some new experiments

Acheson I should like to remind you that the vagus is like an iceberg which shows very little above the surface that these are obviously large fibers with big potentials and that under certain other circumstances they are found to be of little or no consequence as compared with some important reflexes Therefore these fibers may not represent a good sample of the afferents involved in those other reflexes

Moe Isn t it entirely possible that when this nerve is stimulated we are not stimulating the same fibers as those from which potentials were recorded? It is not certain from the evidence you presented that these fibers would fire in response to an increase of atrial pressure or volume It is possible that the fibers which are

receptors, on the venous side of the circulation, whose excitation would accelerate the heart.

The second possibility was suggested by Jarisch and Zotterman (30), and also by Aviado and his colleagues (4). Jarisch and Zotterman stimulated the central ends of the fibers going to the right atrium. Figure 15 will make the anatomy quite clear. The atrial fibers I have just shown you in the cat (Figure 24) were recorded from the nerve, *n II*, in Figure 15. If the peripheral ends of that nerve are cut near the heart and the central ends are stimulated, the only response obtained, according to Jarisch and Zotterman (30), is a fall of blood pressure and heart rate. Jones (19), in my laboratory, recently repeated that procedure and got precisely the same result. Because one obtains only a fall of blood pressure and of heart rate, it seems very unlikely that this could be the afferent pathway of the Bainbridge reflex.

It might be that excitation of these right atrial receptors causes a reflex fall of blood pressure and heart rate. Large doses of veratridine injected into a cat will sensitize the receptors and, as we all know, also cause a fall of blood pressure and heart rate. Although there are many difficulties in establishing this correlation, it is one possibility.

Aviado, and his colleagues (4), observed that raising the pressure in the isolated right heart (including the right atrium, right ventricle, and some tissues attached to them) of dogs causes a fall of blood pressure and heart rate. We do not know where their receptors were. This is an observation that cannot be ignored. I might add that the pressures used were quite high, and that the preparation involved quite a lot of dissection.

The third possibility that has been suggested was one by MacDowall (3). If I may remind you of what sometimes has been called the MacDowall reflex, he observed that in dogs which had been bled, section of the vagi caused a further fall of blood pressure. He therefore suggested that in the vagi there were afferent sensory nerve fibers which served to keep the blood pressure up. He also suggested, although he had little direct evidence to support this view, that this was due to stimulation of sensory nerve endings on the venous side of the circulation. The observations of Neil and his colleagues (58) now suggest that the MacDowall phenomenon may be coming from the chemoreceptors of the aortic arch.

The fourth possibility was the suggestion made by Gauer (5), that perhaps an increase of pressure in the right side of the heart may cause diuresis. If a transfusion is given to an animal, as you

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It might be that excitation of these right atrial receptors causes a reflex fall of blood pressure and heart rate Large doses of veratridine injected into a cat will sensitize the receptors and, as we all know, also cause a fall of blood pressure and heart rate Although there are many difficulties in establishing this correlation, it is one possibility

Aviado, and his colleagues (4), observed that raising the pressure in the isolated right heart (including the right atrium, right ventricle, and some tissues attached to them) of dogs causes a fall of blood pressure and heart rate We do not know where their receptors were This is an observation that cannot be ignored I might add that the pressures used were quite high, and that the preparation involved quite a lot of dissection

The third possibility that has been suggested was one by MacDowall (3) If I may remind you of what sometimes has been called the MacDowall reflex, he observed that in dogs which had been bled, section of the vagi caused a further fall of blood pressure He therefore suggested that in the vagi there were afferent sensory nerve fibers which served to keep the blood pressure up He also suggested, although he had little direct evidence to support this view, that this was due to stimulation of sensory nerve endings on the venous side of the circulation The observations of Neil and his colleagues (58) now suggest that the MacDowall phenomenon may be coming from the chemoreceptors of the aortic arch

The fourth possibility was the suggestion made by Gauer (5), that perhaps an increase of pressure in the right side of the heart may cause diuresis If a transfusion is given to an animal, as you

point with regard to the early stories about the coronary chemoreflex. Amann and Schaefer (57) and Jarisch and Zotterman (30) were all able to show that there was a great increase in the activity of these nerves after injection of veratridine, but inspection of their records shows that the heart was slowed at the same time. I think it is very likely that the vagus of the opposite side was intact, and in that case there was certainly bradycardia. I would have expected therefore a rise in right atrial pressure. Thus it is not surprising that they obtained a great increase in the activity recorded from these nerve fibers.

Comroe: I understand that earlier some of these fibers were thought to come from the pulmonary vessels but they are now believed to come from the atria. What is the present histologic evidence which assures us that they indeed originate in the atria?

Dawes: I do not think histology will provide the answers; it will come from functional evidence.

Comroe: Can one change the pressure in the atria without changing pressure in the ventricles and elsewhere?

Dawes: Yes, I think so. For the details I refer you to the papers by Paintal (8, 31, 32), in which he examined fibers having the activity which Whitteridge (9, 60) regarded as characteristic of pulmonary vascular fibers. As I remember, in one or two experiments their activity increased when a string was drawn around the pulmonary artery, thereby raising the right atrial pressure. Both Paintal and Whitteridge now believe that these pulmonary vascular fibers originate in the atria. This does not exclude the possibility that there are other fibers originating in the pulmonary vessels.

Heymans: Perhaps the difference in responses obtained with changes in atrial pressure may also depend on the condition of the tissue of the atrial wall in which these receptors are situated. Our experiments submitted evidence that the tension and resistance to stretch of the arterial wall where the sinoaortic presso-receptors are situated, are the primary factors affecting these receptors by pressure variations. This could perhaps also apply to the right atrial presso-receptors?

Stead: You mean if we made an atrial wall rigid we might obtain different results?

Heymans: As I shall show later, a change in the tension of the wall in which the presso-receptors are situated shifts the responses to the same change in pressure. These observations are related to the sinoaortic presso-receptors.

Acheson: What about conduction velocity? Do you have evidence

shown to fire when atrial pressure is increased, mediate an increase of pressure and heart rate

Dawes I agree with that, but Jarisch and Zotterman (30), and Jones (19), have used all kinds of durations and strengths of stimuli in an effort to observe pure acceleration of the heart, and they have never seen it Occasionally they have observed a small rise of blood pressure with weak stimulation I think Jones used about thirty cats The principal effect of quite weak stimuli, which is obtained every time, is a fall of blood pressure and heart rate

Heymans Experiments of our laboratory (59) showed an acceleration of the heart induced by increased right atrial pressure This occurs in dogs having a good vagal tone Is it possible that the acceleration did not occur in your experiments because the vagal tone on the heart was already at a very low level, and the heart already accelerated?

Dawes That is a very valuable suggestion

Folkow Is it possible that these receptors on the venous side are of some importance as regards regulations of venous tone and thus of the big venous reservoir? Most of them seem to be activated by increased pressure in the right atrium and the big veins Suppose their discharge induces an inhibition of the vasomotor fibers controlling the tone of the veins, thus automatically lowering the venous pressure again By this I mean an autoregulation of somewhat the same nature as that of the arteriolar tone by way of the carotid and aortic baroceptors This is just a suggestion, but evidently this abundance of receptors must influence *some* effector system

Dawes I have not heard of any experiments which could test that hypothesis

Burch Have you any measurement of the cardiac output? For example, the rate might drop and the output may not change

Dawes Under what conditions?

Burch When the heart slows after stimulation of the central ends of one of these nerves?

Dawes No, we have no information on that

Burton Has the action current been recorded in these nerves when the pressure in the atrium was raised?

Dawes Yes, there is an approximately linear relation between pressure and the frequency of discharge

Stead Can it be made continuous by raising the pressure high enough?

Dawes Yes, certainly For instance, there is quite an important

of the cat he cooled it to 8° C and in so doing blocked the brady cardia and fall of blood pressure which were caused by excitation of the central ends of the nerve However that was only a start further experiments would have to be carried out

Nickerson Can you say anything about what might be called the relative strengths of the various reflexes which bring about a bradycardia and a fall in blood pressure? I am thinking in homeostatic terms now When we administer one of the veratrum alkaloids thereby producing a bradycardia and a rise in atrial pressure if the rise in atrial pressure is in itself a stimulus for the production of a comparable bradycardia theoretically recovery from the veratrum would never occur But it obviously does Are there any data that would give us a sort of balance sheet of the efficacy of these reflexes?

Dawes I do not think there is any quantitative evidence and as yet I am not really convinced of the existence of the second reflex, the fall of blood pressure and heart rate I think it is one of the four hypotheses and I am not prepared even to hazard a guess as to which is the right one

Moe We must not forget that there is a powerful negative feed back mechanism present to take care of the situation surely the carotid sinus reflex will counteract this fall of arterial pressure

Heymans Dont you think that the venous pressure could rise as a result of a fall of pressure in the arterial presso-receptor areas the aortic and carotid sinus?

Burton Am I to understand that there is now a conflict about the facts of the Bainbridge phenomenon and that even its existence is now challenged?

Dawes Yes

Bozler I should like to mention an unpublished experiment in which I tried to approach this problem a little more directly I lowered the intrathoracic pressure by pulling down the diaphragm, and this of course tended to enlarge the great veins and the atria. To avoid the Hering Breuer reflexes the lungs were vagally de nervated Under these conditions a drastic lowering of intrathoracic pressure failed to change blood pressure or heart rate

Comroe How did you denervate the lungs?

Bozler The vagus was dissected free along the hilum of the lungs This was either done bilaterally in a two-stage operation or only on the left side while the right vagus was cut in the neck. Presumably cardiac innervation was completely intact The experiments were carried out two or more weeks after the operation

Selkurt Did you measure the atrial pressure?

as to sensitivity to cold of the fibers, A and B, which you were describing?

Dawes: As far as conduction velocity is concerned, Paintal (8,31, 32) working in Whitteridge's laboratory, measured the conduction velocities. As I recall the figures, the conduction velocities of A, on the average, were slightly higher than those of B. They all ranged from 8 to 17 meters per second. As far as the cold block in which the vagus was concerned, Type A were blocked by cooling to about 8° C., and Type B were blocked by cooling to about 6° C. Probably there was an overlap of the group.

I think one of the important things which Paintal has shown quite conclusively is that in fibers serving the same modality, such as atrial receptors Type A, there is a very wide range of conduction velocities within that group. In the same way, Widdicombe (61,62, 63) has shown that in other vagal afferent nerve fibers, such as the pulmonary stretch receptors of which he has investigated a very large number, the temperature required to block any particular fiber by cooling may vary over a wide range, say from 7° to 18° C. By cooling, only reflexes whose afferent fibers are widely separated may be distinguished.

Acheson: From the facts which were presented, I assume that these are B fibers, and B axons, rather than A or C. I should like to know the relationship to the makeup of the vagus nerve. Probably 85 per cent are C fibers, and 15 per cent A and B fibers.

Dawes: I think Whitteridge is much better qualified than I am to describe the evidence, which is mainly from his laboratory. I think the thesis, which you are putting forward, in general, holds good.

Acheson: Of course, the theory I had in mind may be quite wrong, because there may be only one fiber that controls all the reflex activity one happens to observe. A pronounced effect may be obtained without a great many fibers. It depends upon their connections, doesn't it?

Dawes: Yes.

Alexander: As I understand it, you have been describing the influence of a cold block on the electrical recordings from these afferent fibers. Has anyone carried out the alternative experiment of stimulating the intact nerve in which these fibers are found so as to evoke the reflex response, and has the effect of a cold block been studied on that response?

Dawes: Only to a limited extent, I am afraid. As I remember, when Jones (Figure 15, n II) worked with the right atrial nerve

of the cat he cooled it to 8 C and in so doing blocked the bradycardia and fall of blood pressure which were caused by excitation of the central ends of the nerve However that was only a start further experiments would have to be carried out

Vickerson Can you say anything about what might be called the relative strengths of the various reflexes which bring about a *bradycardia and a fall in blood pressure? I am thinking in homeostatic terms now* When we administer one of the veratrum alkaloids thereby producing a bradycardia and a rise in atrial pressure if the rise in atrial pressure is in itself a stimulus for the production of a comparable bradycardia, theoretically recovery from the veratrum would *never* occur But it obviously does Are there any data that would give us a sort of balance sheet of the efficacy of these reflexes?

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Selkurt Did you measure the atrial pressure?

Bozler The intrathoracic pressure was low

Selkurt You did not take an atrial pressure measure with a manometer?

Bozler No

Dawes An important point would be the difference in pressure between the inside and the outside of the atrium When you pulled the diaphragm down, you altered, in the same sense, both the pressure within the thoracic and that within the atrium You might not have excited the atrial receptors at all

Bozler Would I not have stretched the large veins if intrathoracic pressure had been lowered about 20 mm H_2O?

Dawes Was there any stretch on the walls of the atrium?

Bozler That was just inferred, but I suspect that that is what would happen with such a drastic change in intrathoracic pressure

Dawes Wiggers has emphasized that in order to ascertain the effective (transmural) venous pressure within the chest, one must measure the pressure within the atrium, and the intrathoracic pressure, and estimate the difference

Burton "Transmural pressure," which is the only factor affecting the deformation of the wall, is a very useful term

Fremont-Smith Does it mean the difference in pressure between the inside and outside of the thorax?

Burton Yes, or of any vessel

Heymans We must also remember that the condition of the wall may be changed very easily There is only transmural pressure from both sides, but between those two sides, what else is happening?

Fine One of the things we have been telling students, is that if a person has a perfectly good heart he can be given, intravenously, and fairly rapidly a liter or two of fluid without any noticeable effect on blood pressure or heart rate In that connection, I wonder whether the Bainbridge reflex becomes manifest as a reflex immediately on infusion of fluid into the atrium, or whether it is a response after a large infusion has been completed

Dawes Bainbridge obtained an effect only from very rapid infusions of large quantities of fluid

Fine Any kind of fluid?

Dawes I think he used saline His experiments have been very difficult to repeat, and there is a great deal of conflicting evidence regarding the Bainbridge reflex Many different techniques have been used in attempts to raise the atrial pressure without the complication of infusing large quantities of fluid, which may be acting

further on the circulation No one I think has demonstrated a satisfactory experiment

Fremont Smith When large quantities of fluid are rapidly infused would a slight change in the temperature of the fluid be a danger point in that experiment?

Dawes Certainly but I think most people have controlled that

Fremont Smith Did Bainbridge?

Dawes I think so yes

Burton There is a paper by Schroeder and Brehm (64) which claims that the reflex effect on the venous side of the heart does not depend upon the absolute pressure in the atrium but upon the gradient of pressure along the inferior vena cava. You see this would give us a way out If the receptors which they examined had to work in conjunction with some others lower down and it was the difference between the pressures at the two places that controlled the reflex, then one would expect that raising the pressure at the heart end would have the opposite effect from the Bainbridge reflex

Burch Dr Dawes does pressure or direct stretching in the vicinity of the atria, vary the rate of the impulses recorded other than by reflex mechanisms?

Dawes I do not know

Burch There could be thermal influences

Dawes Yes undoubtedly

Nickerson Particularly on the venous side small changes in the vasomotor tone may be much more important in changing the tension on the vessel wall than the volume of the contents We know that these vessels can change their capacity tremendously without much alteration in pressure I think venomotor tone may be one of the factors that has been inadequately controlled or evaluated in most of these experiments Inasmuch as it is probably the actual tension on the wall, whether generated by mechanical factors within the lumen or by the dynamic contraction of the smooth muscle of the wall itself which activates baroreceptors it may be impossible to reconcile these experiments until some method is devised to control or evaluate this tension

Alexander I should like to know about the degree of adaptation in these afferents a point which may have some bearing on the question Dr Fine raised a few moments ago There are many examples in neurophysiology of important positive feedback systems but they are usually rapidly adapting If there is a rapidly adapting effect we have an entirely different homeostatic picture

than we do when there is a factor which is not adapting but is acting continuously

Dawes I do not know of any systematic studies on the adaptation rates of these particular fibers, but there is an impression that they are slowly adapting The only information about them is contained in the article by Dickinson (10)

Green Dr Little (65), at our institution, became interested, a few years ago, in whether there was any correlation between venous pressure and other factors that might occur in heart failure He found that the best correlation he could obtain was between venous pressure and venous oxygen tension, rather than between venous pressure and blood volume or other factors He wondered whether there might be some chemoreceptor on the venous side of the system to sense this oxygen tension

Dawes It would be interesting in the fetus, would it not, because in that case the inferior vena cava is full of blood that is 60 per cent saturated with oxygen However, I know of no evidence of the existence of such a chemoreceptor

Nickerson The oxygen tension problem, of course, brings up the possibility of local as well as reflex factors I am thinking particularly of the coronary circulation, where evidence is accumulating that almost irrespective of the factor varied, the rate of flow is inversely proportional to the amount of oxygen carried by the blood This applies to partial saturation, anemia, and other conditions

THE MOE AND GRUHZIT REFLEX*

Moe I might say, by way of introduction, that the extra vagal reflex (Table IV, Number 8) does not replace, but may supplement, the "headquarters reflex" of Dr Heymans I do not believe that it was developed for the control of arterial pressure in the sense that the carotid sinus and the aortic reflexes serve that function

The reflex is elicited by the intravenous administration of epinephrine, which produces, in addition to a multitude of other effects, an increase of the blood flow through the extremities I presume that the increase is largely in the muscles, although in these studies we have not separated muscle from other tissue Thus, when I speak of an increase in peripheral blood flow, I am referring to an increase

*The experiments described represent, in large part, the work of Dr Carl Gruhzit, Dr Walter Freyburger, and other colleagues The work was begun in the Department of Pharmacology of the University of Michigan, and continued in the Department of Physiology of the State University of New York, Medical Center, at Syracuse Generous support has been provided by the Life Insurance Medical Research Fund

of blood flow in the femoral artery of the dog Our experiments have been designed primarily to define the afferent mechanism of this reflex and so far little has been done with that mechanism

When epinephrine is given and a rise of arterial pressure occurs part of the resulting vasodilation must be due to the action of the increased pressure upon the carotid sinus and upon the arch of the aorta. However if one denervates these structures by sectioning both carotid nerves and both vagi in the neck the intravenous injection of epinephrine will still provoke an increase of the blood flow in the leg

It is well known that epinephrine is capable in itself upon intra arterial administration of dilating arterioles and hence increasing blood flow again primarily in muscular vascular beds It therefore becomes important in studying the reflex components which persist in the absence of the carotid sinus and aortic arch mechanism to eliminate the direct effect of epinephrine upon arterial vessels This of course can be very simply accomplished by perfusing the extremity from another animal without interrupting the nerve supply to that extremity Most of the crucial experiments I shall describe were done in this way The leg was perfused from another animal the perfusion pressure in that leg was kept constant and access of epinephrine to the vessels of that leg was excluded If the leg is perfused in such a fashion and if the carotid nerves and both vagi are sectioned, administration of epinephrine into the trunk of the recipient animal still causes a very considerable vasodilation in the perfused member We have not made many quantitative studies because with the flowmeter we have used for these studies we were interested primarily in qualitative effects However I should guess the increase of blood flow is of the order of from 200 to 300 per cent We were a little disturbed that vagal section did not interrupt this reflex because one of our first ideas was that epinephrine exerted its action by way of the coronary chemoreflex which Dr Dawes has already described

Figure 25 shows that, considering latency and other factors this is almost certainly not the coronary chemoreflex To test this possi bility we used procedures similar to those of Dr Dawes although not quite so elegantly performed All experiments were done in dogs

At the first signal 2 μg of epinephrine were injected into the left descending coronary artery which was cannulated close to its junction with the circumflex artery The upper record is that of arterial pressure the lower is that of blood flow in the femoral artery In this experiment the femoral artery was not perfused from

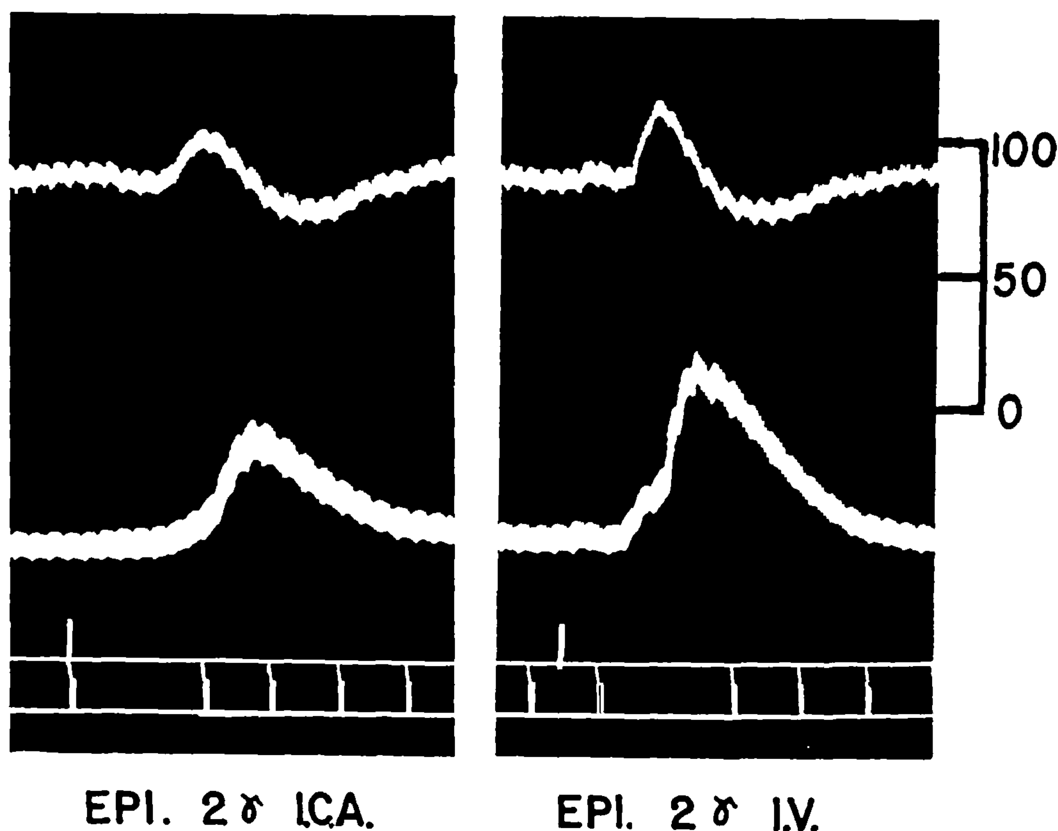


FIGURE 25 Arterial pressure (top), and femoral arterial blood flow in a dog under barbital anesthesia Left anterior descending coronary artery cannulated and perfused from a carotid artery At the first signal, epinephrine was injected into the coronary perfusion line At the second signal, same dose was injected intravenously Time, 10-second intervals (gap at 1 minute)

another animal When epinephrine was injected into the coronary circulation, there was vasodilation in the leg, but it occurred after a latency of from 15 to 20 seconds, too long to suggest a direct action of epinephrine on a coronary chemoreceptor mechanism

On the right side of the figure we see the response and the latency to the same dose of epinephrine given intravenously The response was greater, and the latency shorter, than that observed after injection into the coronary circulation This seems to eliminate the coronary reflex as a major cause of the reflex dilation in the leg

Burch Was there a record of the volume of the limb?

Moe No, this is a flow record recorded with a differential manometer A small trace of epinephrine could enter the leg, but in most experiments it does not occur

Heymans We have done these experiments One may completely cut off, without any leak, the flow of blood between the leg and the donor However, the nerves still connect the leg with the donor dog

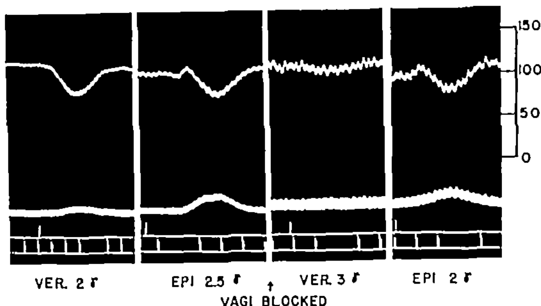


FIGURE 26. Arterial pressure (top) and femoral arterial blood flow in dog under barbital. Other conditions as in Figure 25. All injections were made into the coronary perfusion line. Time 10 seconds.

Moe Figure 26 illustrates another test of the coronary chemoreflex possibility. The upper record is of arterial pressure, the lower is of femoral blood flow. The drugs were injected into the descending ramus of the left coronary artery. Veratridine in a dose of 2 μg produced a fall of arterial pressure and a slight increase of leg blood flow. I suspect that the reason the response was less than in your experiments, Dr Dawes, is that you cannulated the central trunk instead of the descending branch.

Dawes I quite agree with that.

Moe Epinephrine in a dose of 2.5 μg injected into the same artery produced a similar fall of arterial pressure and a somewhat greater increase of blood flow, but notice that the latency was greater than for veratridine.

Then the vagi were blocked. They were not cooled to a measured temperature but they were surrounded by broad copper hooks projecting from an ice bath. A larger dose of veratridine now failed to cause a response but a smaller dose of epinephrine still provoked a characteristic one. Thus this response to epinephrine is not mediated by the vagus nerves and cannot be an example of the coronary chemoreflex. I might say that this disappointed us because we were hopeful that epinephrine might prove to be the physiological stimulus of the coronary receptors.

Having established that the reflex dilation is not the result of activation of the "headquarters" receptors in the aorta and the carotids, and is not an example of the coronary chemoreflex, we sought next to assess the role of arterial pressure changes, thinking that perhaps secondary presso-receptors in the systemic arteries might be involved In a number of experiments in which arterial pressure was controlled by means of a pressure stabilizer, intravenous epinephrine regularly caused vasodilation in the perfused

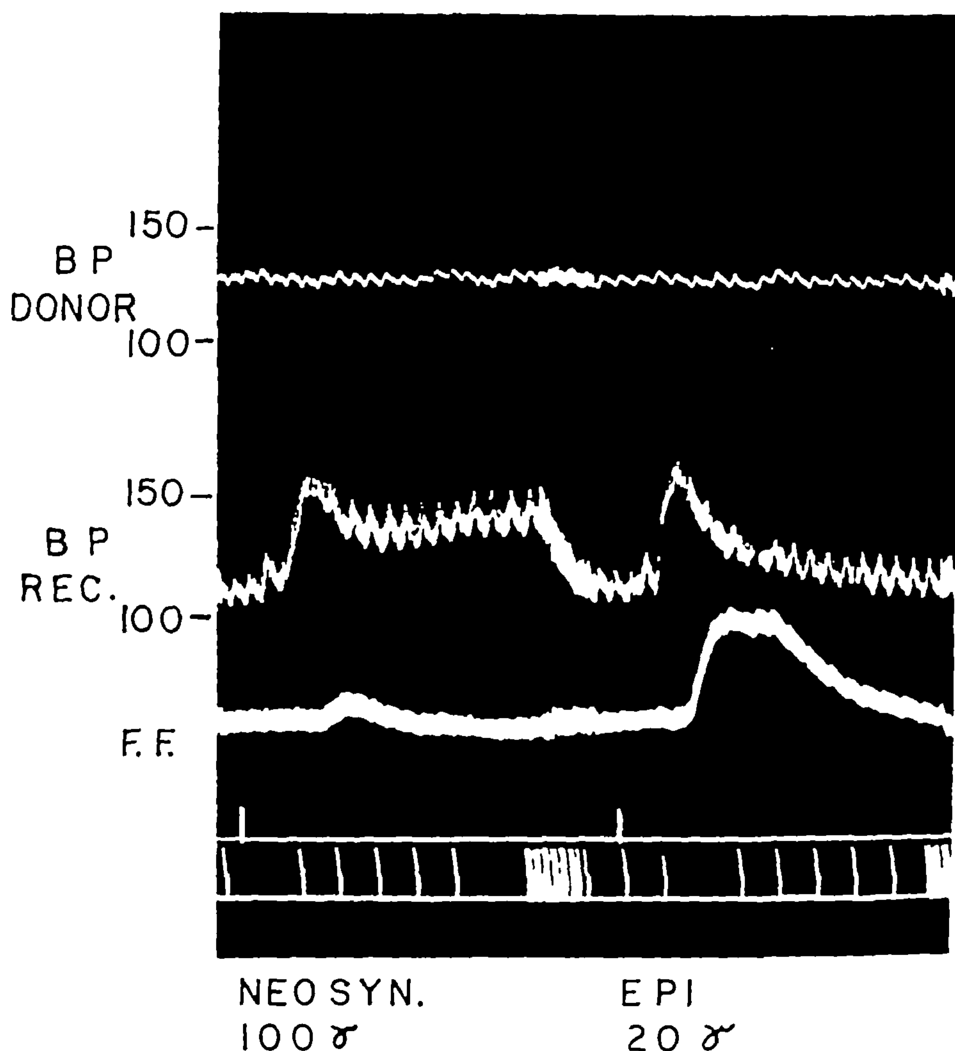


FIGURE 27 Cross circulation experiment, both dogs under barbital anesthesia and heparinized Top tracing, arterial pressure of donor dog, middle tracing, arterial pressure of recipient, lower tracing, femoral arterial blood flow in recipient leg perfused from donor animal. Nerve supply of perfused leg intact, vagi and carotid nerves of recipient animal sectioned At signals, 100 μg of phenylephrine (neosynephrine), and 20 μg of epinephrine, total dose, intravenously in recipient animal Time, 10 seconds

extremity without significant elevation of aortic pressure Furthermore artificially induced elevation of the pressure achieved by rapidly increasing the pressure in the stabilizer in animals deprived of their carotid and aortic nerves caused only slight elevation of blood flow in the perfused leg

Another bit of evidence which eliminates the arterial pressure as a factor is illustrated in Figure 27 in which we compared epinephrine with phenylephrine (neosynephrine) In this experiment the leg was perfused from a donor animal whose blood pressure is shown at the top The arterial pressure in the trunk of the recipient animal is shown in the center tracing The lower one again is the blood flow in the innervated perfused extremity Phenylephrine in a dose of 100 μg caused very little dilation in the leg A smaller dose of epinephrine chosen to produce essentially the same elevation of arterial pressure although of briefer duration produced a very significant increase of blood flow in the perfused extremity

Fremont Smith I might add one experiment on man carried out in 1926 by Arlie Bock and Henry Field of the Massachusetts General Hospital They gave epinephrine intravenously measured blood flow in the limb and I think arterial oxygen retention in venous blood and they showed that the increase of blood flow in the arm long outlasted the rise in systolic blood pressure In fact it continued for some 40 minutes when they were dealing essentially with a lower blood pressure Certainly the diastolic pressure was considerably down

Moe Although the reflex dilation is apparently independent of changes in systemic arterial pressure the possibility remains that pressure changes elsewhere in the circulation could activate tension receptors which would mediate this vasodilation in skeletal muscle We looked next to the pressure in the atria and in the pulmonary artery knowing that intravenous injection of epinephrine often elevates the pressure in these chambers

Figure 28 illustrates two such experiments In the first half of this figure 20 μg of epinephrine were given At the top we have the arterial pressure in the center the blood flow in the femoral artery at the bottom, the pressures in the left atrium (*LAP*) and the right atrium (*RAP*) The leg was not perfused in this experiment, but the carotids were denervated and the vagi cut, so that the headquarters reflexes were eliminated. Epinephrine provoked the expected increase of blood flow in the femoral artery but

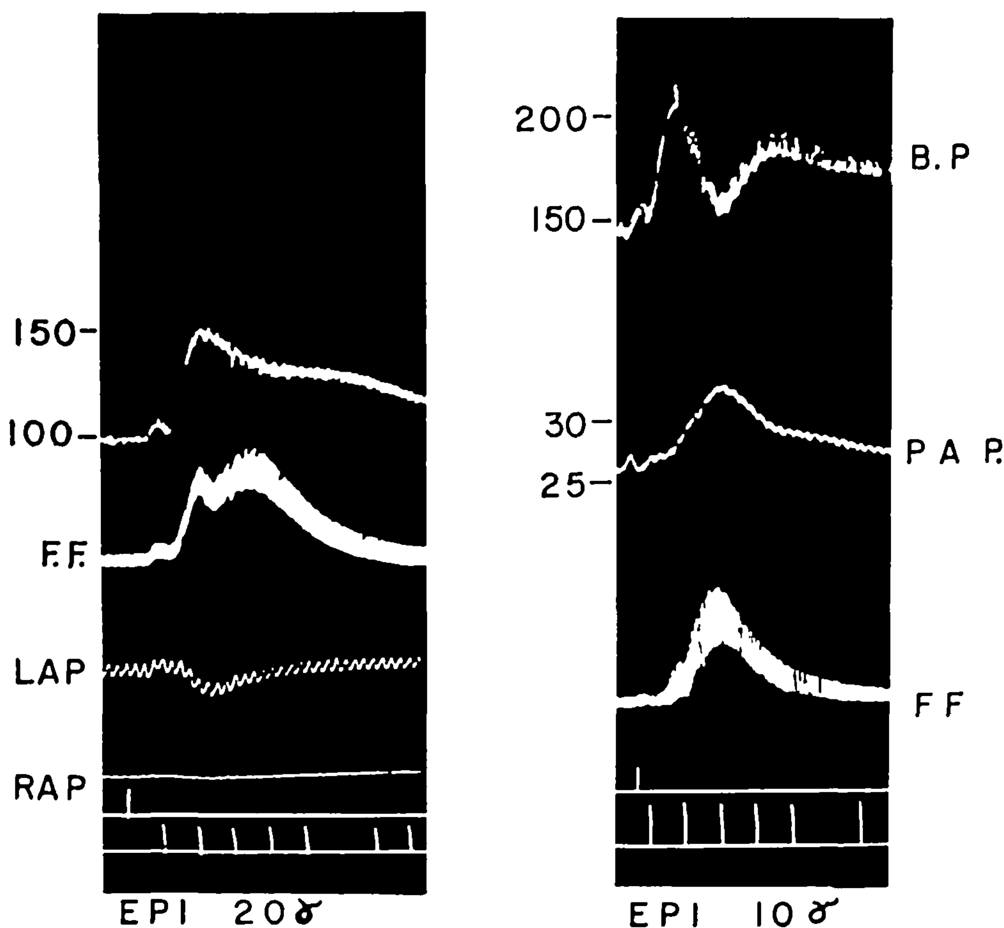


FIGURE 28 Two experiments, both on dogs under barbital Tracings on the left, from top to bottom arterial presssure, femoral arterial blood flow, left atrial pressure, right atrial pressure, signal, time (10 seconds) Right-hand tracings arterial pressure, pulmonary arterial pressure, femoral arterial blood flow Vagi and carotid nerves cut At signals, epinephrine injected intravenously

lowered the pressure in the left atrium and did not alter the pressure in the right atrium

In the experiment illustrated in the second half of the figure, we see that the increase of blood flow (lower tracing), in response to 10 μg of epinephrine, was essentially simultaneous with the pulmonary arterial pressure response, which is the center record If this blood flow response is due to the increase of pulmonary arterial pressure, then it should also appear when blood or saline is rapidly infused into the right atrium to provoke an increase of pulmonary pressure This was tried in the experiment illustrated in Figure 29

In this experiment the leg was perfused from another animal whose pressure is shown in the top tracing The other three tracings

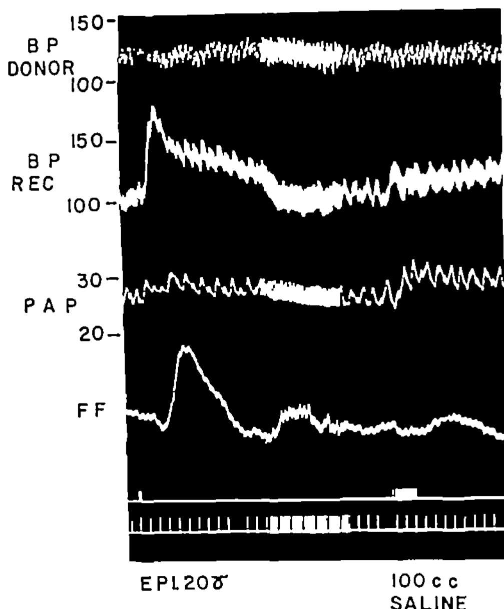


FIGURE 29 Cross circulation both dogs under barbital heparinized. Tracings, top to bottom, arterial pressure of donor arterial pressure of recipient, pulmonary arterial pressure of recipient, femoral arterial blood flow of recipient leg perfused from donor Vagi and carotid nerves of recipient cut. Injections of epinephrine and saline intravenously Time, 5 seconds.

are in order arterial pressure and pulmonary arterial pressure of the recipient animal, and blood flow in its perfused leg. Twenty μg of epinephrine leading to a very slight increase of pulmonary arterial pressure in this instance caused a great increase of blood flow One hundred ml. of saline given rapidly enough to cause a greater increase of pulmonary arterial pressure failed to change the femoral blood flow significantly Thus the reflex cannot be due to an increase of mean pressure in the pulmonary artery

At the next stage in our investigations, since the reflex was not mediated through the vagus nerves, we attempted to find out just what nerves did serve as the afferent pathway The next group of figures shows the pertinent experiments

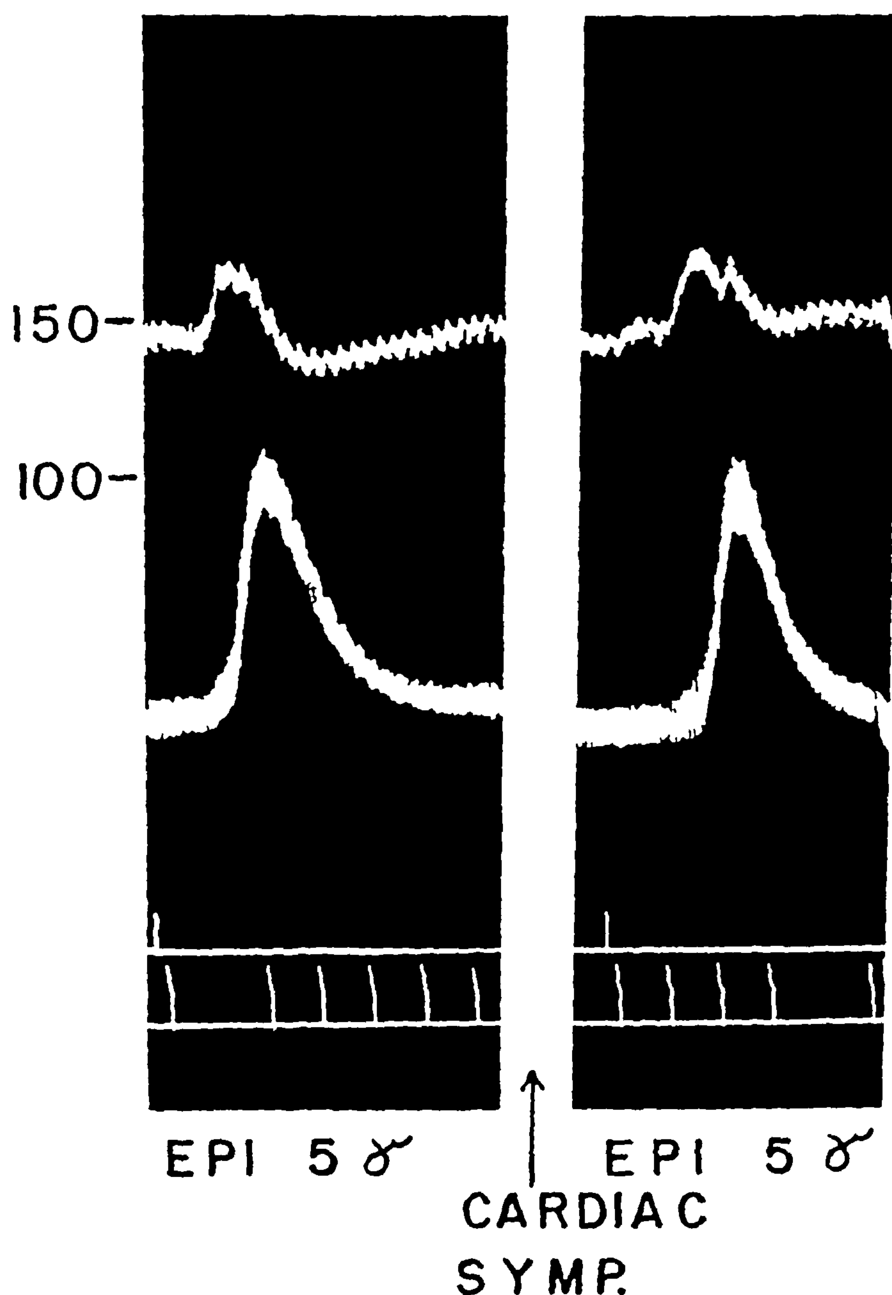


FIGURE 30 Arterial pressure (top), and femoral blood flow in dog under barbital Vagi and carotid nerves cut At signals, 5 μg epinephrine (total dose) intravenously Between segments ("cardiac symp"), lower cervical and upper thoracic sympathetic ganglia excised

Figure 30 shows the response to a dose of 5 µg of epinephrine injected intravenously before and after removal of the upper four or five thoracic sympathetic ganglia including the stellates on both sides The vagi of course were already cut With the heart "de centralized" the blood flow response persisted undiminished

In further experiments even more ruthless denervation was attempted In addition to the vagi and the thoracic sympathetics the phrenic nerves and branches of the brachial plexus were cut and the esophagus and trachea were transected at the apex of the thorax. Reflex dilation in the leg was still obtained.

If the afferent limb of this reflex does not leave the chest through the vagi or sympathetics it might be doubted whether it originates in the chest at all However the reflex can be induced by intra venous administration of epinephrine by injection into the pul monary artery into the left atrium, and into the cavity of the left ventricle but it cannot be induced by injection into the arch of the aorta. *If epinephrine is injected directly into the aorta so that it does* not traverse the cardiac circulation it causes an increase of pressure but it does not lead to reflex vasodilation This observation suggests *but admittedly does not prove that the receptor elements lie within* the thorax The only remaining pathway by which afferent impulses could leave the chest must be the somatic nerves of the thorax.

In the next series of experiments we explored that possibility Dogs were prepared by exposure of the spinal cord from the last cervical to the first lumbar segment. Loose ligatures were passed under all the thoracic dorsal roots on both sides The dogs were then turned over with the strings hanging out so that they could be quickly pulled out to break all the dorsal roots One hind leg was prepared for perfusion from a donor dog the carotid sinuses were denervated and the vagi were cut.

Figure 31 illustrates such an experiment At the top is the donor animal's pressure below that the pressure of the recipient animal, and below that the blood flow in the perfused femoral vascular bed.

The first two segments show the response to 5 and 10 µg doses of epinephrine injected intravenously into this semi intact dog There was as you see a moderate increase of arterial pressure and an increase in the rate of blood flow through the perfused leg Between the second and third segments of the figure all of the thoracic dorsal roots were pulled out at once The response of the arterial pressure to epinephrine was at least as great, and in fact in most experiments was greater after dorsal root section, but the blood flow response was abolished.

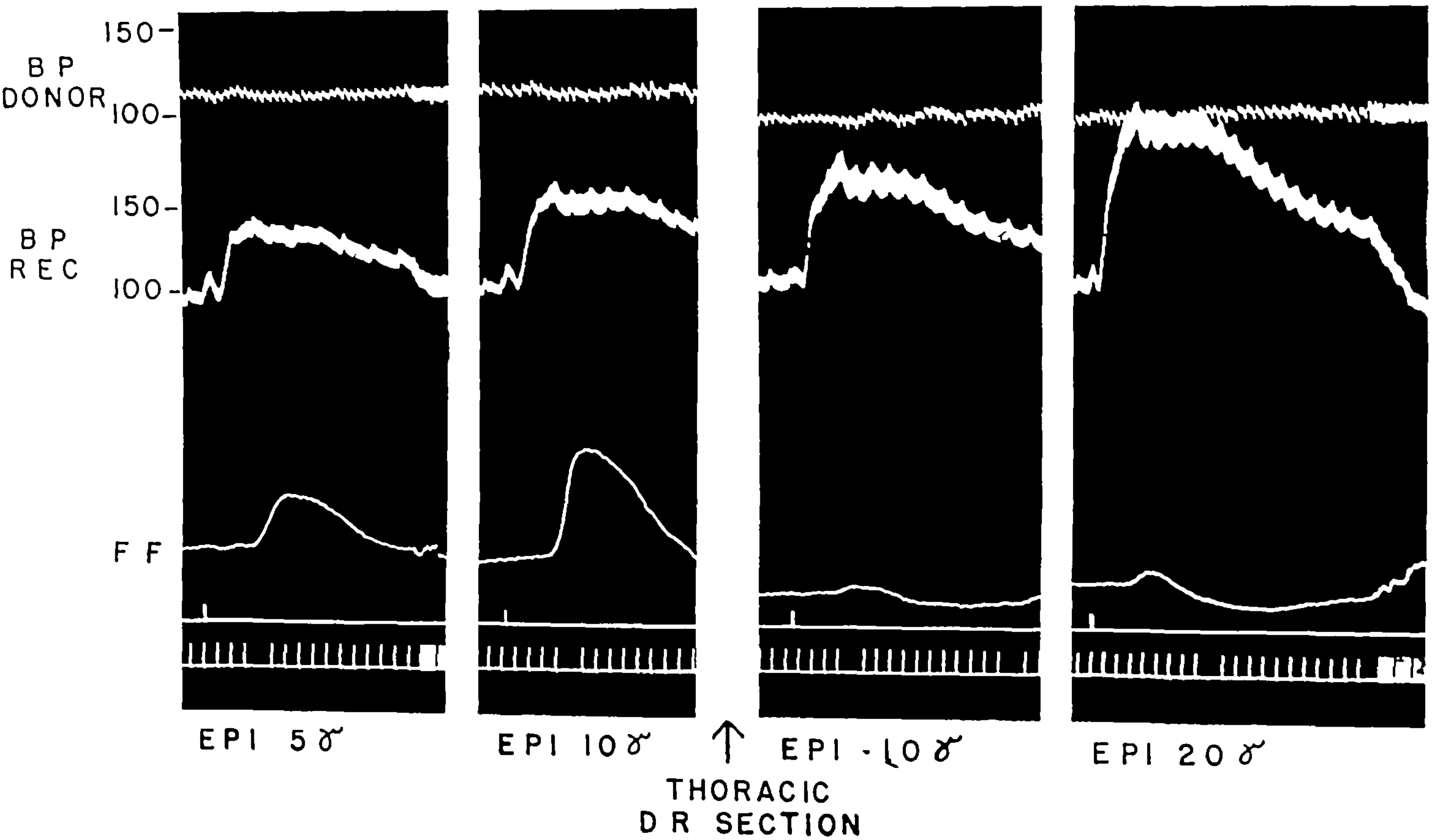


FIGURE 31 Cross circulation experiment, both dogs under barbital Arterial pressure of donor and recipient dogs, femoral arterial blood flow in recipient leg perfused from donor dog Vagi and carotid nerves cut Thoracic dorsal roots of recipient dog exposed, cut bilaterally at arrow Epinephrine injected intravenously in recipient dog

In other experiments the dorsal roots were cut stepwise the response to epinephrine being checked at each step in order to determine at what segments afferent impulses entered the cord Whether root section was performed segmentally from the top down or from the bottom up the reflex dilation was totally abolished only when all thoracic roots had been cut Therefore whatever these afferent fibers are and from wherever they originate they enter the spinal cord diffusely probably through all of the thoracic segments. That, unfortunately makes it very difficult to trace further their precise anatomical course It would be much more convenient if they were in one little bundle that could be traced into the spinal cord

The dorsal root section experiments support the belief that the reflex originates within the chest, but tell us little about the nature of the receptor elements These could be chemoreceptors within the cardiac or pulmonary circulation but the diffuse distribution of the afferent fibers suggested that mechanoreceptors within the aorta, or its intercostal branches might be involved Since elevation of the aortic pressure by means of a pressure stabilizer or by intraortic injection of epinephrine itself does not evoke the reflex the hypothetical mechanoreceptors would have to be endowed with the property of rapid adaptation unlike the classical "headquarters" receptors of the carotid sinuses that is they might respond to the increased pulse pressure or increased cardiac stroke output induced by epinephrine, but fail to respond effectively to a sustained elevation of mean arterial pressure If this hypothesis is valid it follows that epinephrine would have to traverse the coronary circulation in order to elicit the response it also follows that exclusion of the receptor area, i e the thoracic aorta should eliminate the reflex

Figure 32 illustrates a rather elaborate experiment set up to test the latter hypothesis The aorta was ligated just above the diaphragm its subdiaphragmatic branches were supplied with blood through a tube connecting an iliac artery (centrally cannulated) to the left subclavin artery The leg below the iliac cannula was perfused from another animal whose pressure is indicated in the uppermost tracing The thoracic aorta could be opened or closed at will by application of a clamp just beyond the left subclavian The vagi and carotid nerves were cut.

At the first signal in Figure 32, epinephrine was injected intravenously into the recipient animal the aorta being open down to the ligature at the diaphragm Reflex vasodilation occurred in the perfused leg The second injection given while the aorta was

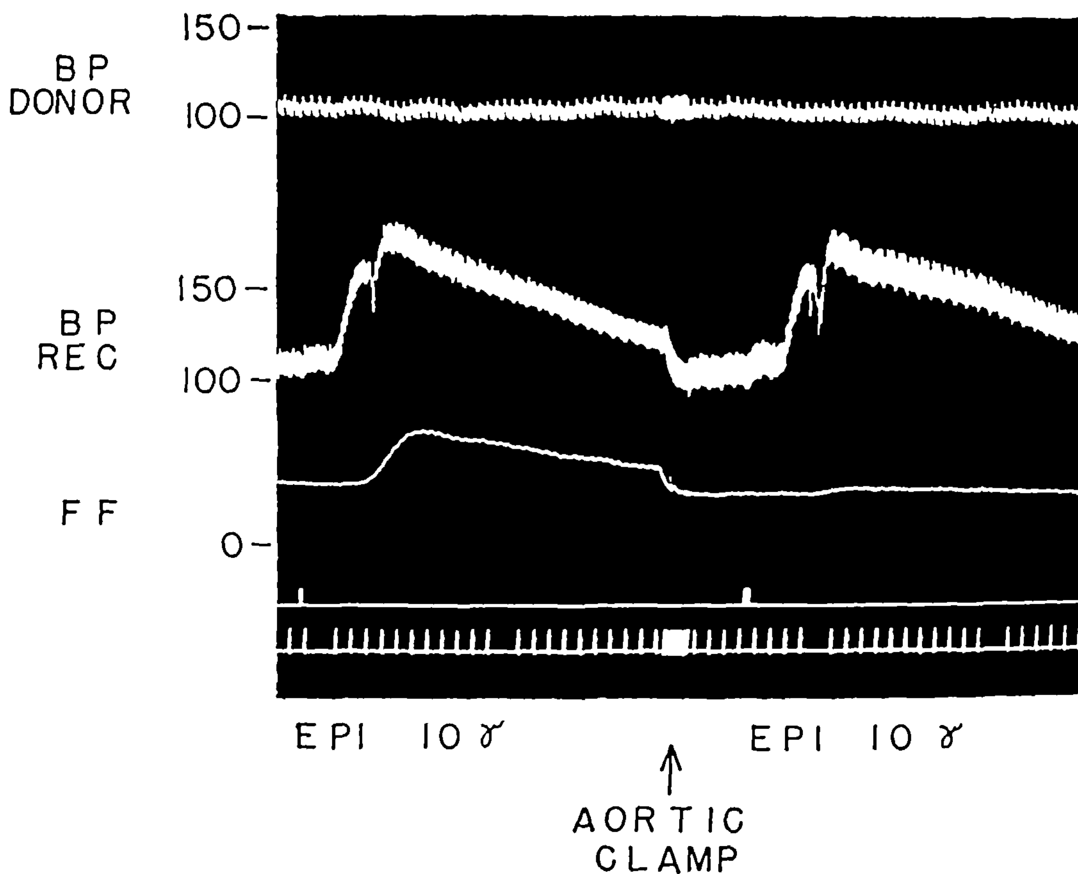


FIGURE 32 Cross circulation experiment, both dogs under barbital Arterial pressure of donor, arterial pressure of recipient, and femoral blood flow of recipient Vagi and carotid nerves cut At first signal, epinephrine injected intravenously, thoracic aorta open At second signal, same dose with thoracic aorta excluded between left subclavian artery and the diaphragm Time, 5 seconds

clamped, failed to initiate the reflex, although the pressor response was just as great In this instance only the arch of the aorta was exposed to the presumed mechanical effect of cardiac stimulation

This suggested that there must be some kind of receptor in the aorta or in the neighborhood of the aorta which was stimulated by the increased vigor or frequency of cardiac contraction If this is true, then suitable mechanical stimulation of the aorta, not induced by epinephrine, should also cause femoral dilation In the experiment just described, rhythmical tugging on the ligature about the aorta above the diaphragm caused the blood flow rate in the perfused leg to increase I should also like to point out that we have not eliminated the heart itself as a contributory source However, it is not the only source, because the heart was functioning in the experiment shown in the second half of Figure 32 just as it was in the first, but the reflex is gone

Fremont Smith How did you tug on the aorta?

Moe The chest was open In this experiment the aorta was tied above the diaphragm and we *just pulled on the string* anteriorly and caudally

Fremont Smith You were dislocating the aorta laterally not longitudinally

Moe There must be components in both directions If tension is put on the ligature and held no response is obtained If one tugs on it rhythmically there will be a sustained increase in blood flow in the leg

Burch Did you try an artificial pump?

Moe We tried perfusing the thoracic aorta from a pump in a rather complicated experiment in which we could alternate between steady and pulsatile perfusion pressure There was an increase of blood flow but essentially the experiment was disappointing We did obtain a response but it was not very great

Heymans We have been interested in the same problem Experiments published in 1936-1937 (12 13 14) showed that in the dog deprived of vagi aortic and carotid sinus nerves increase and decrease of arterial blood pressure still cause respectively vasodilation and vasoconstriction in the spleen kidney and leg In the experiments these three organs were isolated from the circulation in dog B and were perfused by another dog A The innervation of the organs remained intact and the vasomotor reactions were registered. Rise of arterial pressure in dog B by intravenous injections of saline blood epinephrine ephedrine or synephrine induced dilation in all three organs Decrease of arterial pressure by hemorrhage provoked the opposite reaction

These vasomotor responses induced by alterations of arterial pressure were present in the spinal dog, produced by decapitation and *in the dog deprived of his sympathetic ganglia from the stellate* to the fifth thoracic ganglia The responses disappeared however after destruction of the spinal cord and after excision of all sympathetic ganglia Further experiments showed that variations of arterial pressure in the mesenteric circulation provoked reflex vasomotor reactions

Presso-receptors inducing vasomotor responses are located in the lower part of the thoracic aorta, in the origin of the coeliac and in the mesenteric arteries However these vasomotor reflexes which adapt vascular tone to the systemic arterial pressure do not play an important part in the homeostatic regulation of the systemic arterial pressure as do the presso receptive areas in the aortic arch

and carotid sinus They may conceivably have a more far-reaching role in the local or regional distribution of blood, and in a minor and accessory manner may join with the sinoaortic reflexes in the regulation of the systemic arterial pressure The observations of Marrazzi (66) indicate that the responses induced by epinephrine are due, at least in part, to its action on synaptic transmission

Fremont-Smith Can it be done by changing the pressure alone, without epinephrine?

Heymans Yes, the same may be obtained by raising the blood pressure with an intravenous injection of saline

Dawes In this respect it differs from the observations of Dr Moe, who showed clearly that a change of mean pressure did not produce the effect that he was interested in

Heymans We also observed that injection of small amounts of epinephrine, although it does not affect the systemic blood pressure, induces reflex dilation in the perfused spleen and leg However, because the systemic blood pressure is not increased, I do not think it means that blood pressure may not be increased in the mesenteric circulation We know that the mesenteric, more than other blood vessels, react to epinephrine, by constriction I quite agree with Dr Moe that epinephrine induces a more marked reaction in the perfused leg than does a rise of pressure induced mechanically, or by injection of other hypertensive drugs It is possible that besides the rise of pressure provoked by epinephrine, some specific action of the drug may also play a role

In the light of Marrazzi's observations (66), we considered that our so-called reflex was due to interruption or depression of transmission in the ganglia of the efferent pathway Being somewhat sensitive to ganglionic blocking agents anyway, this was one of the first explanations we considered It was for that reason that in some experiments we injected epinephrine directly into the arch of the aorta, from which site it surely has access to the lumbar ganglia, and to the mesenteric branches of the aorta However, we never observed femoral vasodilation in response to intraaortic injections Thus, what we have demonstrated here is, I am sure, a reflex I do not know whether it goes up to the brain, and it may very well not It could be mediated through the spinal cord itself, but I have no comment about that However, our observations cannot be explained by interruption of ganglionic transmission, nor by change of pressure alone

Stead Did you increase the pulse pressure?

Moe That is one of the things we thought might affect receptors

in the thoracic aorta We considered the possibility that there might be rapidly adapting tension receptors which were not stimulated by sustained elevation of pressure We do not have any evidence whatever for that. I think it would be necessary to study the afferent nerves electrically but if they are so diffuse they would be quite inaccessible.

Nickerson Do you have a suggestion of diffuseness from the string experiment?

Moe A suggestion but that is all

Alexander What is the status of the pericardium in these experiments?

Moe The reflex will occur with the pericardium open and it will also occur after administration of procaine into the pericardial sac

Stead How long does the reflex last? If a continuous infusion of epinephrine is given is a sustained effect obtained or does it just die away?

Moe I do not think we have ever done that I do not know what would happen.

Heymans The experiments show that the reflex vasodilation is related to the rise in blood pressure The two curves of rise in blood pressure induced by epinephrine and reflex vasodilation indeed run parallel. Raising the arterial pressure by other means induces the same responses

Stead Did you give the epinephrine over a period of minutes and was the vasodilation sustained?

Heymans The vasodilation sustains as long as the pressure is high

Stead An hour or half an hour?

Heymans We did not give epinephrine over a long period, but one intravenous injection or infusion over a short period If small amounts of epinephrine are injected, no rise of systemic arterial pressure occurs but a reflex vasodilation may still occur in the perfused innervated spleen of the spinal dog

We suggested that although the systemic arterial pressure does not raise, the mesenteric vasoconstriction induced by epinephrine, could still induce a rise of mesenteric arterial pressure acting on the presso-receptors located in the mesenteric area, and provoke a reflex vasodilation in the spleen But we have still to keep in mind the possibility of a decrease of synaptic transmission caused by epinephrine as shown by Marrazzi.

Green We have frequently noticed quite marked dilation if

when we are trying to stimulate the sympathetic chain, we simply pull a little bit on the chain or on the intestine I wonder if what we are stimulating is not a very widespread receptor of some sort, that responds to a mechanical distortion in a large number of places over the viscera

Moe In the thorax, at least, the dilation is eliminated by a thoracic dorsal root section Whether that applies to the abdominal viscera, I do not know, but at least it pins a major share of the afferent source of the response down to the thorax It is my guess that this is a response of mechanical receptors in the thoracic distribution of the aorta, not necessarily in the wall of the aorta, but perhaps in the periaortic connective tissue

If one drags stimulating electrodes up and down the posterior thoracic wall adjacent to the aorta, one also obtains dilation of the femoral artery, but that is a very nonspecific and crude experiment I admit it does not prove anything If one applies a local anesthetic by spreading soaked cotton pledgets along both sides of the aorta within the chest, the reflex disappears, although other reflexes persist The reflex may be restored by washing out the chest cavity with warm saline

Folkow I wonder whether this reflex vasodilation of the limb is abolished by sympathectomy of that limb? All other types of true reflex vasodilations, except a few within specific tissues supplied by the cranial or sacral parasympathetic vasodilator fibers, are, to the best of my knowledge, abolished by sympathectomy

Moe I should guess that it is so, but we have not cut the sympathetics in dogs in which the limb was perfused from another animal

Folkow The reflex vasodilation obtained by stimulation of the baroreceptor regions is solely due to an inhibition of constrictor tone, and thus completely abolished by sympathectomy

Moe It is my guess that that would be true in this case, but we do not have enough experiments to be certain of it

Heymans Our experiments showed that reflex vasodilation is abolished by sympathectomy The efferent pathways provoked by rise of blood pressure in the spinal dog, and in the dog deprived of his sinoaortic and vagi nerves, thus are located in the sympathetic

Burton Dr Moe, does atropine knock out this efferent pathway of the receptor mechanism?

Moe Atropine does not abolish the response, which again leads me to believe that it would be abolished by sympathectomy, as Dr Heymans has stated

Folkow It seems reasonable that atropine does not abolish this

reflex response if like most other vasodilator reflexes it is due to an inhibition of the prevailing constrictor tone and does not involve the sympathetic vasodilator fibers which are activated in other types of reaction patterns Experiments on the vasodilator fibers have shown that they are not involved in the reflexes responsible for blood pressure homeostasis

Although it is not really applicable to the present topic I should like to present a figure illustrating the extremely marked effects that these sympathetic vasodilator fibers may induce on the blood flow through the muscles Figure 33 shows the blood flow through the muscles of the cat s limb Stimulation of the abdominal sympathetic trunk activates the vasomotor fibers to the vessels of the limb but the constrictor fibers are blocked by dihydroergotamine revealing the large dilator response evoked by the cholinergic vasodilator fibers A stimulation frequency of six per second increases the blood flow roughly five times and a maximal dilation of the blood vessels is obtained if the stimulation frequency is slightly increased. Expressed in other terms the peripheral resistance is then decreased to about one seventh of the original value a very dramatic change These sympathetic dilator fibers whose action is easily blocked by minute amounts of atropine may be activated from structures in anterior parts of the hypothalamus and Uvnäs and others (67 68 69 70 71 72 73 74) were recently able to activate them from the cerebral cortex in close connection to the motor area. It seems not improbable that they are activated under emergency circumstances possibly also during muscular work, to accomplish the best possible blood supply to the working muscles in the initial phases of activity The evidence for this is not definite and conclusive but it seems to be well established that they are not engaged in blood pressure homeostasis as such Anyhow these fibers must have some function and the hypotheses I mentioned seem to be the only alternatives left This figure illustrates the striking vascular effects that may be produced by these previously not very well known fibers when activated separately

Moe I did not understand why you gave dihydroergotamine

Folkow The abdominal sympathetic trunk carries both dilator and constrictor fibers to the vessels of the limb muscles The action of the constrictor mediator may be eliminated by dihydroergotamine and stimulation of the mixed trunk will then only induce the effect of the dilator fibers which as they are cholinergic can be blocked in a similar way by atropine

Green Dr Folkow we have confirmed this work by using other

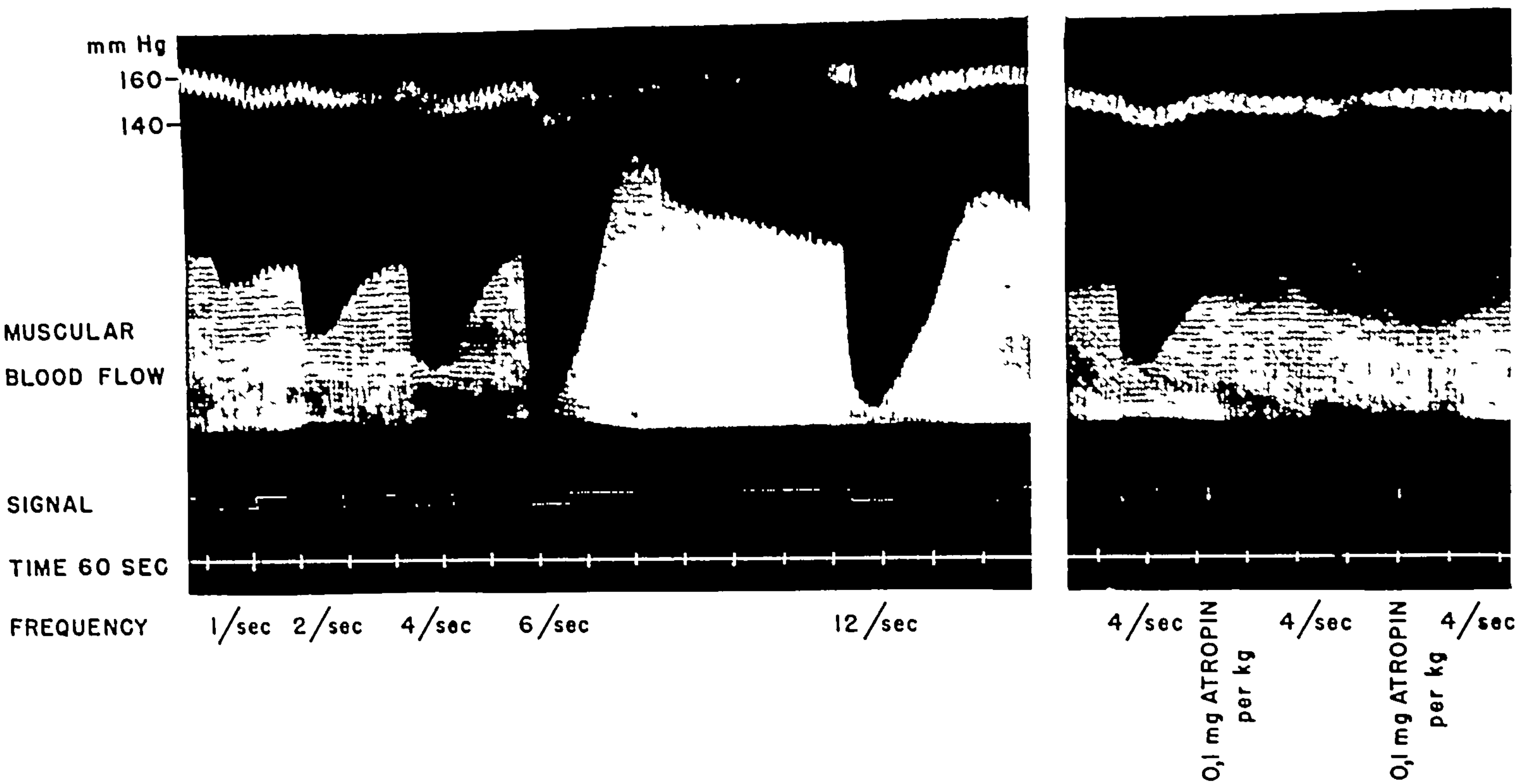


FIGURE 33 The effect of the cholinergic sympathetic vasodilator fibers on the blood flow through the muscles of the hind limb of the cat The blood flow is measured by a drop recorder that operates an ordinate writer, the ordinates being inversely proportional to the rate of flow Reprinted, by permission, from Folkow, B Impulse frequency in sympathetic vasometer fibres correlated to the release and elimination of the transmitter *Acta physiol scandinav* **25**, *49 (1952)*

adrenergic blocking drugs but have noted that the dilator response appears to fatigue much more readily than the constrictor response The latter is present as long as one stimulates for 30 seconds or a minute whereas under the same stimulus the dilator response lasts perhaps 10 or 15 seconds and then dies out. Has that been your experience?

Folkow In general yes when the mixed sympathetic trunk is stimulated

Green Under conditions in which the constriction is abolished by adrenergic blockade one still has a short lasting dilator response

Folkow As I remember from our experiments the constrictor fibers are often difficult to block totally at least when higher stimulation rates are applied By more selective activation of the dilator fibers from their hypothalamic representation I have a feeling that the dilator responses may more easily be continued but we have not studied this particular problem to any more extensive degree as we generally stimulated for rather short periods only We were mainly interested in obtaining reproducible responses so we have not observed a clear cut effect of atropine The hypothalamic structures are easily damaged so for this reason we restricted the stimulation periods I think one may keep a rather steady dilation for up to one minute and perhaps much longer if one is careful.

Green Do you find that also true when you stimulate the sympathetic chain?

Folkow If I stimulate the sympathetic trunks in an animal given ergotamine or dihydroergotamine (the stimulation frequency is as high as 20) it is very difficult to block completely the constrictor effect which builds up more and more during the course of the stimulation period, probably due to an excess accumulation of the mediator substance This slowly rising constrictor effect may be part of the explanation why the dilator fiber effect soon diminishes

Green With an adrenergic blocking drug, such as ilidar or dibenamine one may block the constrictor response completely

Folkow I think another factor of importance is the stimulation frequency applied The rates generally used from 20 to 30 per second are probably far above the physiological discharge rates Fiber systems stimulated at rates far higher than the normal ones are apt to show signs of exhaustion, probably first in the synaptic transmission mechanism. The preganglionic fibers release a given quantum of acetylcholine at every excitation if the rate is too high the amount released at each stimulus might diminish At the

moment the amount becomes subthreshold, due to exhaustion, the ganglionic transmission will fail and thus also the activity of the postganglionic fibers It is not impossible that the dilator fibers are more easily exhausted than the constrictor fibers by high frequencies A prolonged effect might be obtained with very low rates Whatever the explanation, I think it is our necessarily rather crude experimental methods which are the chief cause of the vanishing dilator response

THE PRESSO-RECEPTORS OF THE CAROTID SINUS

Dawes I think we should ask Dr Heymans to say something about his recent investigations into the presso-receptors in the carotid sinus, because these are observations which may have a bearing on different types of reflexes and receptors

Heymans It is well known that the aortic and carotid sinus nerves are not only the means of the reflex blood pressure regulation, but also the reflex buffer nerves of the systemic arterial pressure This reflex regulation of blood pressure occurs by the action of the arterial pressure itself on receptors located in the wall of the sinoaortic areas Experiments of Koch (75), Heymans and coworkers (76), and Hauss and associates (77), submitted evidence that arterial pressure does not act directly on the sinoaortic receptors, but indirectly by acting on the wall of the arteries where these receptors are located

These experimental observations suggest that the tone, tension and distensibility of the arterial wall of the sinoaortic areas could play a role in the mechanisms of reflex regulation of blood pressure This suggestion has been investigated in a series of experiments in order to examine the influence on arterial pressure, and on the reflex regulation of blood pressure, of alterations in tension, resistance to stretch and distensibility of the sinoaortic vascular wall For this purpose, drugs believed to contract or relax the arterial wall were applied locally to the carotid sinus, and to the aortic pressoreceptive areas

The experiments were performed on dogs anesthetized with morphine-chloralose In a first series of experiments, the vagi-aortic nerves were cut in order to limit the reflex regulation of blood pressure to the receptors of the carotid sinus areas The systemic arterial pressure was registered from a femoral artery The blood pressure reflexes of carotid sinus origin were elicited by clamping and unclamping both common carotid arteries The drugs were applied locally by injection of their solutions into the conjunctival space surrounding both carotid sinus areas

The experiments showed (78 79 80 81 82 83 84 85 86) that epinephrine, norepinephrine, diacetylepinephrine thiosulfonic acid, synephrin, ephedrine, hydroxyphenylamino-propanal and hydroxytryptamine (serotonin) applied locally to the arterial wall of the carotid sinus provoke a marked fall of the systemic arterial pressure and a reduction or suppression of the hypertension reflexes normally elicited by decrease of intracarotid sinus pressure. These reactions are due to a stimulation of the carotid sinus pressoreceptors. Indeed, section of the carotid sinus nerves, when the systemic arterial pressure has been lowered by the local application of the drugs to the carotid sinus, provokes an immediate and very marked rise of the systemic arterial pressure. Figure 34 represents the curves of a typical experiment with norepinephrine. Our experiments showed further that smooth muscle relaxing drugs such as

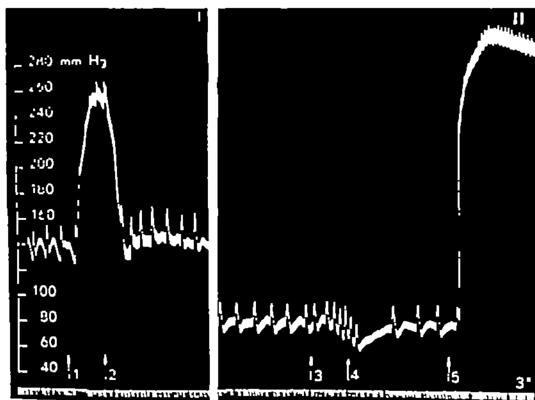


FIGURE 34. Dog, 27 kg., anesthetized with morphine-chloralosane. Both vagi aortic nerves cut. Registration of blood pressure from femoral artery. 1, 2: Clamping and unclamping of common carotid arteries. Between *I* and *II* local application of 0.25 ml. norepinephrine, 1 per cent on carotid sinuses. 3, 4: Clamping and unclamping of common carotid arteries. 5: Section of carotid sinus nerves. Reprinted, by permission, from Heymans, C., and van den Heuvel Heymans, G. Action of drugs on arterial wall of carotid sinus and blood pressure. *Arch. internat. pharmacodyn.* 83: 520 (1950).

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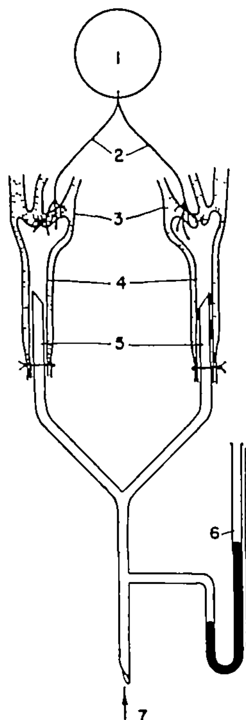


FIGURE 36. Diagram of method used for carotid sinus preparation. *1* Vasomotor centers. *2* Carotid sinus nerves. *3* Carotid sinus. *4* Venous balloon in carotid sinus. *5* Cannula tying balloon and common carotid artery. *6*: Manometer for recording pressure in balloon and carotid sinus. *7* Tube connected with pressure recorder. Reprinted, by permission, from Heymans, C., Delaunois, A. L., and van den Heuvel-Heymans, G. Tension and distensibility of carotid sinus wall, pressoceptors and blood pressure regulation. *Circul Res* 1 3 (1953).

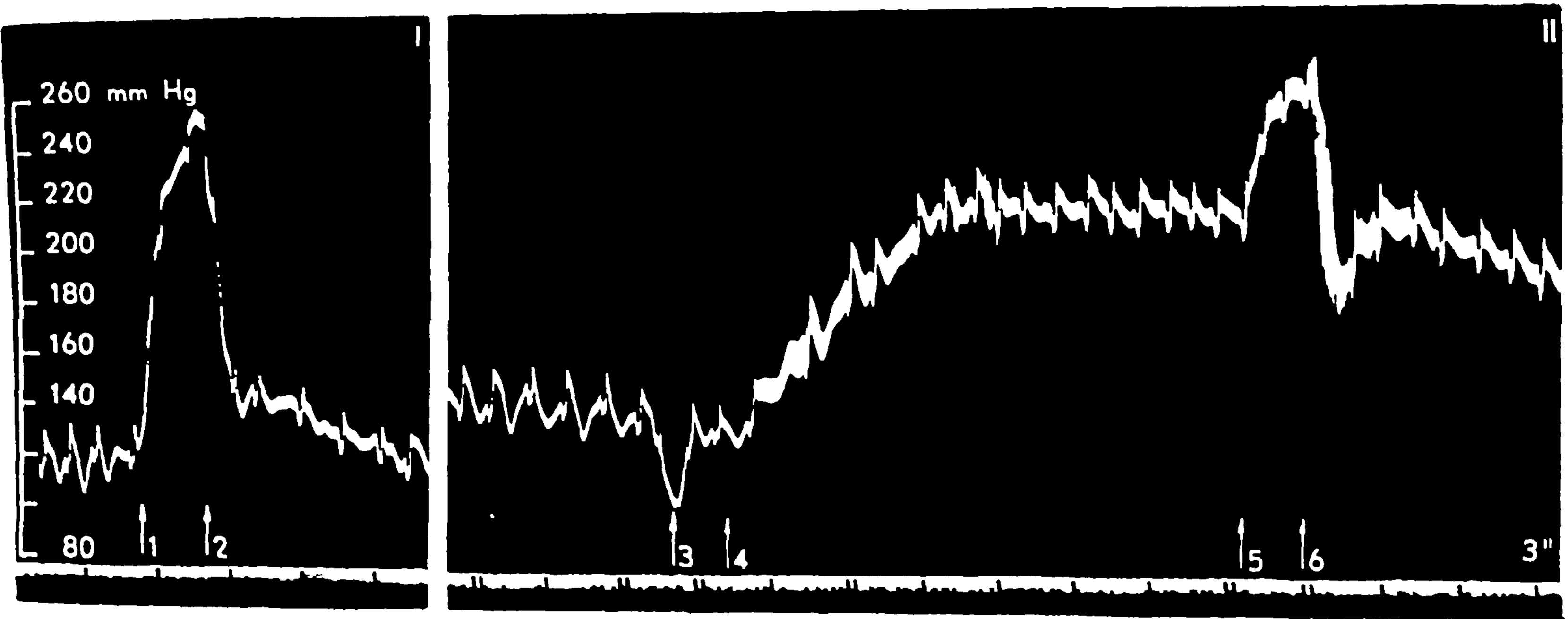
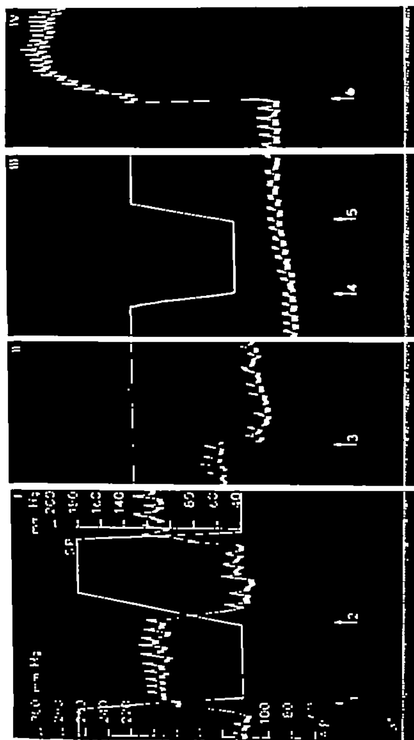


FIGURE 35 Dog, 23 kg, anesthetized with morphine-chloralosane Both vagi-aortic nerves cut Registration of blood pressure from femoral artery *1 - 2* Clamping and unclamping of common carotid arteries *3 - 4* Local application of 0 25 ml benzylimidazoline hydrochl 1 per cent on carotid sinuses *5 - 6* Clamping and unclamping of common carotid arteries Reprinted, by permission, from Heymans, C, and van den Heuvel-Heymans, G Action of drugs on arterial wall of carotid sinus and blood pressure *Arch internat pharmacodyn* **83**, *520 (1950)*



papaverine, potassium chloride and benzylimidazoline, applied locally to the wall of the arteries of the carotid sinus, induce a reflex rise of the systemic arterial pressure Figure 35 represents the curves of an experiment with benzylimidazoline

These experiments submitted evidence that drugs contracting the arterial wall of the carotid sinus, increasing its tension and resistance to stretch, cause stimulation of the receptors of the carotid sinus This stimulation induces reflexly a fall of the systemic arterial pressure, and decreases or suppresses the responses of the receptors to a decrease of pressure Drugs relaxing the arterial wall of the carotid sinus, decreasing their tension and resistance to stretch, reduce the stimulation of the presso-receptors and thus induce a reflex rise of the systemic arterial pressure

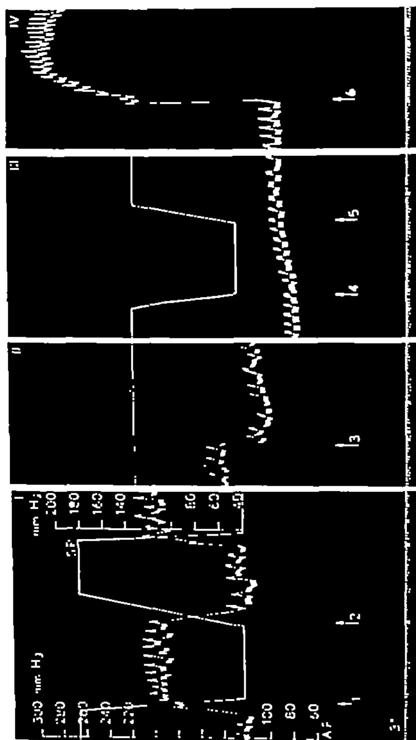
Landgren, Neil and Zotterman (84) confirmed our observations on cats with epinephrine, norepinephrine, and vasopressin, and also showed that local carotid sinus application of these drugs elicits a very definite increase of the presso-receptors, impulse traffic Sodium nitrite, administered locally to the carotid sinus areas, causes, on the contrary, a marked reduction of the presso-receptor's activity

Landgren (87) concluded from his experiments on the isolated carotid sinus preparation of cats, that local application of epinephrine causes a contraction and a decrease of distensibility of the carotid sinus arterial wall at low intrasinusal pressure ranges, but an increase of distensibility in the region of the physiologic intrasinusal pressure range (from 80 to 180 mm Hg)

However, our experiments on dogs (88), showed that the same blood pressure reactions induced by local carotid sinus application of norepinephrine occur *in vivo* at different physiologic and nonphysiologic intrasinusal pressure ranges (Figures 36 and 37) They demonstrated further (85,89) that epinephrine and norepinephrine,

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FIGURE 37 Dog weighing 15 5 kg Carotid sinuses prepared according to method shown in Figure 36 Blood pressure from femoral artery (*AP*) Pressure in venous balloon and carotid sinuses (*SP*) *1 - 2* Lowering and raising intrasinusal pressure caused hypertensive and hypotensive vasomotor reflexes *3* Local application of 20 μg norepinephrine on each carotid sinus, while maintaining constant intrasinusal pressure at 130 mm Hg, caused fall of systemic arterial pressure from 140 to 80 mm Hg *4 - 5* Five minutes after local carotid sinus application of norepinephrine, lowering and raising intrasinusal pressure caused no response in systemic arterial pressure *6* Forty-five minutes after local carotid sinus application of norepinephrine, section of both carotid sinus nerves induced hypertension Reprinted, by permission, from Heymans, C, Delaunois, A L, and van den Heuvel-Heymans, G Tension and distensibility of carotid sinus wall, pressoceptors and blood pressure regulation *Circul Res* I, 3 (1953)



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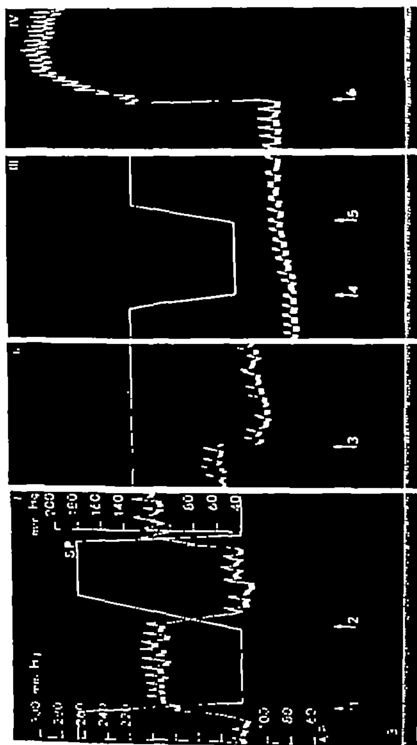
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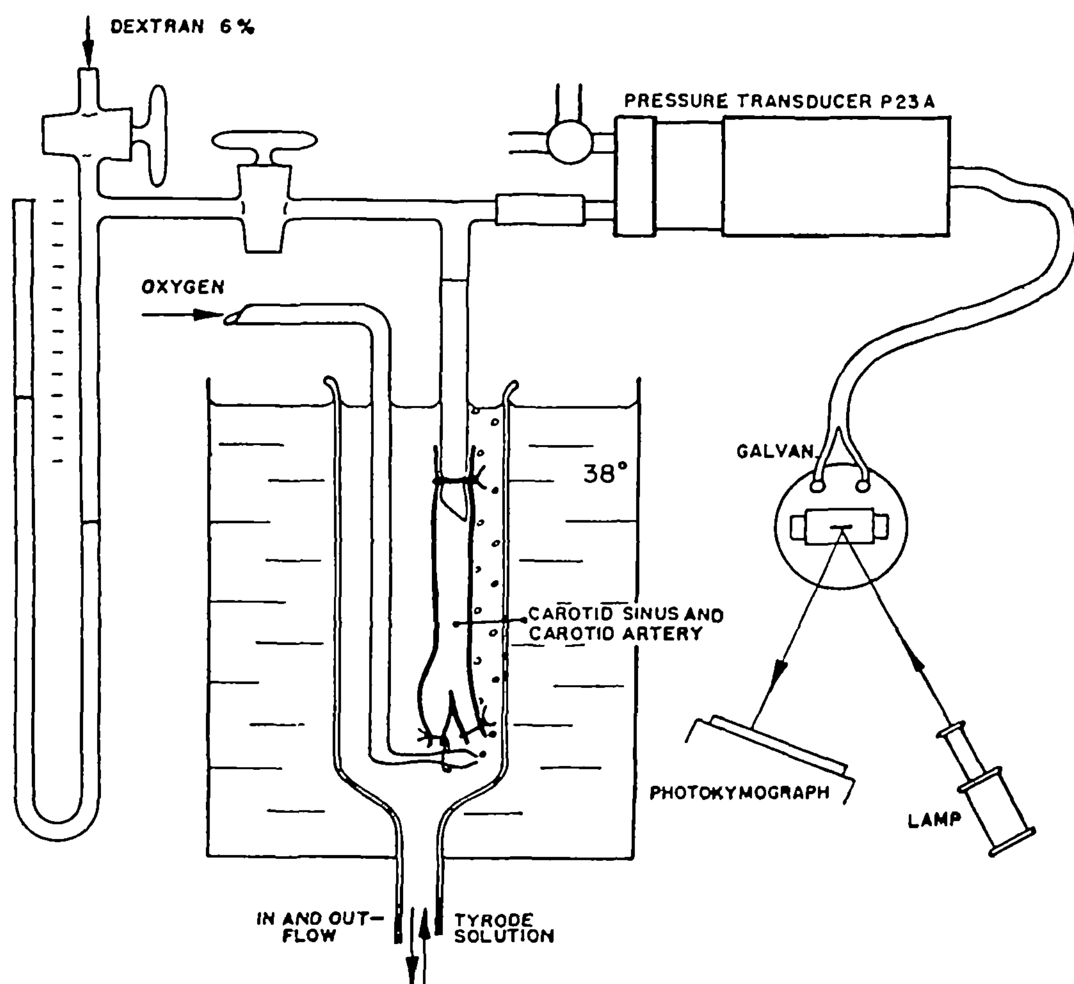


FIGURE 38 Technique used for the measurement of the internal pressure-response variations of the isolated carotid sinus and carotid artery preparation Reprinted, by permission, from Heymans, C, and Delaunois, A L Action of drugs on pressure-response and distensibility of carotid sinus arterial wall *Arch internat pharmacodyn* **96**, *99 (1954)*

acting on the isolated carotid sinus preparation of dogs, induce a contraction of the carotid sinus arterial wall, an increase of their pressure-response, and a decrease of their distensibility The same reaction occurs at different low, normal and high intrasinusal pressure ranges (Figures 38 and 39) Benzylimidazoline induces, on the contrary, a decrease of pressure-response, due to a relaxation and increase of distensibility of the carotid sinus arterial wall (Figure 40) Experiments of de Vleeschhouwer, Martini and Calliauw (90) in our laboratory, showed that local application of epinephrine or norephinephrine on the aortic-arch presso-receptive area, also provokes a reflex fall of the systemic arterial pressure

It was concluded from these different series of experiments that

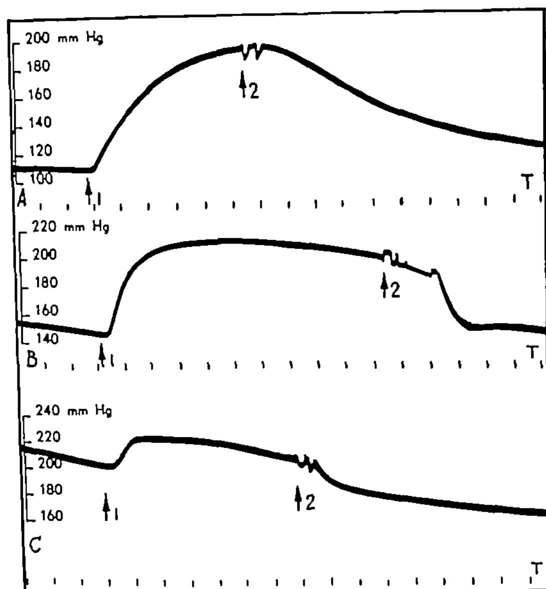


FIGURE 39 Increase of internal pressure-response in carotid sinus preparation due to norepinephrine A At a steady internal pressure of 108 mm. Hg, the internal pressure rises to 195 mm. Hg. *B* At a steady internal pressure of 150 mm. Hg, the internal pressure rises to 226 mm. Hg. *C* At a steady internal pressure of 200 mm Hg, the internal pressure rises to 230 mm. Hg. At ↑1 addition of norepinephrine to Tyrode's solution, in concentration 2.10^{-6} At ↑2 washing out with Tyrode's solution T Time in minutes. Reprinted, by permission, from Heymans C and Delaunois, A. I Action of drugs on pressure-response and distensibility of carotid sinus arterial wall. *Arch internat pharmacodyn.* 96, 99 (1954)

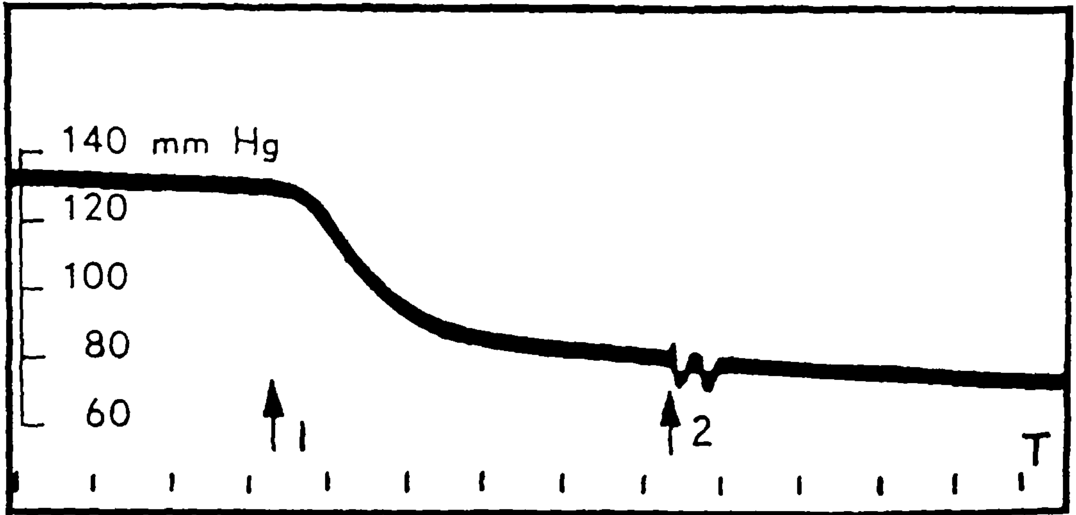


FIGURE 40 Decrease of internal pressure-response in carotid sinus preparation due to benzylimidazoline (priscoline) in concentration of 2 10^{-5} At ↑1 addition of benzylimidazoline to Tyrode's solution At ↑2 washing out with Tyrode's solution T Time in minutes Reprinted, by permission, from Heymans, C, and Delaunois, A L Action of drugs on pressure-response and distensibility of carotid sinus arterial wall *Arch internat pharmacodyn* **96**, 99 (1954)

the state of contraction and tension, and thus the *resistance to* stretch of the arterial wall where the sinoaortic receptors are located, are the primary factors affecting these receptors which regulate reflexly the systemic arterial pressure These findings emphasize the fundamental role of the biologic condition of the sinoaortic arterial wall in the reflex regulation and homeostasis of blood pressure I am convinced, by the experimental data, that the condition of the arterial wall of the presso-receptive areas is more important than the pressure for the reflex regulation of arterial pressure Alterations in tension and resistance to stretch of the sinoaortic arterial wall change profoundly the responsiveness of the presso-receptors to pressure variations

Comroe You mean this is a true presso-receptor, and not a stretch or volume receptor? In other words, it is sensitive to the squeezing of the muscle in the wall?

Heymans I should say that the sinoaortic receptors behave as receptors sensitive to the tension of the arterial wall This tension depends on the pressure on the wall and on the resistance of the wall to be stretched by the pressure The sinoaortic receptors thus behave and react, in some way, as the muscle spindles

Knisely May I point out that vessel walls have an internal circulatory system, the *vasa vasorum* These are necessary for the preservation of the normal healthy functioning anatomy of the walls of

the large vessels Ramsey (91) and O Neill (92) demonstrated that the *vasa vasorum* are necessary to maintain the anatomy and Samuels *et al* (93) presented methods of study

Burch I should like to ask Dr Heymans if he would expect the same response in any other artery

Heymans Experiments of Emmel and Smith (94) demonstrated on isolated segments of arteries of dogs that local application of epinephrine induces an increased pressure response due to con traction of the arterial wall.

Burch Then it is not peculiar to that artery?

Heymans Different arteries react in the same manner to epineph rine but as the different elements of the arterial wall of the carotid sinus seem to be in series it is quite possible that the responsiveness of this arterial wall may be more marked than in other arteries

Dawes I do not think you have yet proved your proposition that these are presso-receptors rather than stretch receptors It seems to me that the phenomenon you have observed could be explained if the receptors were in series with the muscular elements If a drug were applied to the arterial wall which caused the muscular elements to contract, and if any of the sensory receptors were in series with those muscular elements they would be incited to con tinuous activity In the lax condition when the drug is not applied and the arterial wall is pulsating equally well pulsations will be transmitted to those sensory receptors I think that this may well be the explanation of this phenomenon.

Heymans It is of course a possibility

Dawes We have no histologic evidence on it.

Heymans The responses of the arterial wall to pressure and to pressure variations at different ranges are related to physiological and biophysical questions I think Dr Burton could help us to clear up the biophysical side of the problem Anyway the experi mental data show that not the stretch of the arterial wall by pres sure but the tension of the arterial wall provoked by the intrinsic tone of the wall on one hand and the pressure to the wall on the other is the fundamental factor in the stimulation of the sinoaortic receptors regulating reflexly the arterial pressure Information con cerning the mechanisms maintaining, and affecting, the intrinsic tone and tension of the arterial wall are very limited

Folkow I should like to draw attention to the papers of Landgren (87 95) I think at least I can remember the results I believe he presented evidence of two different types of baroreceptors one of them parallel to the muscle cells the other in series with these

cells This arrangement means that contraction of the smooth muscles in the sinus region will activate the series-coupled receptors, while distension of the vessel will activate both sets of receptors I think this hypothesis will fit in very well with the experimental results of Dr Heymans

Comroe I do not like to bring the word "shock' into this conference, but when there is a prolonged fall in blood pressure, main arteries contract as well as arterioles and venules Under these circumstances, it would seem to me that we obtain inhibition of the vasomotor center instead of lack of inhibition This may explain a number of the phenomena that are known as "irreversible" shock I am wondering what the opinion of the group is on that particular matter Might this explain the relaxation of vessels that occurs after vasoconstriction or might this have something to do with the reputed effect of dibenamine and other peripheral blocking agents in the treatment of experimental shock?

Burton Zotterman and Landgren (84,87,95), published quantitative biophysical details on the ideas which Professor Heymans had They were working with him As I remember, they demonstrated in their experiments that the blood pressure did not change at all times They were recording the action currents, and they showed that by application of these drugs, the sensitivity to a given change in blood pressure is greatly altered They correlated that quantitatively with the volume pressure relationships, and with the distensibility in the aorta, which is itself changed, of course, when these drugs are applied So when the sensitivity to a change in pressure is increased by the use of a drug, locally applied, it correlates with an increased stretch of the wall for the same blood pressure From a biophysical point of view, therefore, I feel that results are being obtained along the lines that Professor Heymans has presented

Green This response is somewhat analogous to the response reported in Montreal at the Symposium on the Behavior of Spiral Fibers in Skeletal Muscle (96) According to this report, when the fiber contracts it seems to increase the sensitivity of the spiral endings

Were there comparable changes in heart rate along with the changes in blood pressure that you recorded?

Heymans If norepinephrine is applied locally to the carotid sinus areas of dogs with vagi nerves intact, a slowing of the heart also occurs, along with the fall in arterial pressure This bradycardia is of reflex origin Section of the carotid sinus nerves, or of

the vagi nerves suppresses the bradycardia. The stimulation of the carotid sinus receptors induced by local application of norephinephrine, thus provokes a reflex drop of blood pressure and a reflex slowing of the heart

Green Is it possible that in essential hypertension there might be something that acts like a dilator on the walls of the carotid sinus?

Heymans Drugs relaxing the arterial wall where the receptors of the buffer nerves of arterial pressure are situated shift the systemic blood pressure to a higher level and thus induce hypertension These observations suggest that decrease of tension and resistance to stretch of the sinoaortic arterial wall could be the primary mechanism of hypertension

Nickerson I wonder whether we can obtain some information on the hypertension question without going directly to the carotid sinus We know that in the type of hypertension induced by sodium nitrite applied to the wall of the carotid sinus or in older experiments induced by denervation of the carotid sinus the rise in blood pressure is quite sensitive to adrenergic blocking agents I think Dr Heymans showed this originally with ergot and it has been repeated with dibenamine and many other drugs since that time

The rise is completely eliminated and the animal is returned to an essentially normal pressure by these agents The average patient with hypertension simply does not respond that way The fall in pressure is highly variable from one patient to another and in the majority much less than a complete reduction is obtained I think we can use this as indirect evidence that a strictly neurogenic mechanism is probably not of major importance in the majority of these cases

Heymans In acute neurogenic hypertension, induced in dogs by cutting the aortic nerves and lowering the intracarotid sinus pressure local application of norepinephrine to the carotid sinus areas induces a fall of systemic arterial pressure In chronic hypertension induced by renal ischemia, local carotid sinus application of norepinephrine also provokes a fall of arterial pressure However do not take my data as definite because only a small number of experiments have been performed.

Fremont Smith Dr Heymans in your experiment shown in Figure 39 was there a steady pressure in the carotid sinus or was it pulsating?

Heymans It was a steady pressure

Fremont Smith It seems to me the experiment might have to

be repeated with a pulsating pressure in the carotid sinus, not only because of the lateral dilation, which I think we tend to give too much emphasis to, but perhaps even more for the longitudinal stretch of the aorta

Heymans A steady pressure in the carotid sinus keeps the responses of the presso-receptors going quite normally during a long period Steady pressure used in some of our experiments does not alter, I think, the responsiveness of the carotid sinus receptors In most of our experiments, the pressure in the carotid sinus was pulsating, and the responses were identical

Knisely From a consideration of these two sets of factors, a new direction of investigation on high blood pressure could easily start On the basis of the remarks made by Dr Burton on the positions of the physical receptors, I think two factors ought to be investigated as soon as possible the shifts in the coefficients of the elasticity of the walls, and in the capability of the walls to receive nutrition Well-known histopathology of selected vascular areas may be shifting adjustments of the whole system over a period of years

Shorr Dr Dawes, would you be willing to give us a summary, and if so, Dr Fine has requested that you discuss these reflexes in relation to their possible function in homeostasis

SUMMARY

Dawes It is clear that from this work has emerged a principle which is very important, since it appears to apply not only to the stretch receptors, or those in the carotid sinus, but also to the atrial receptors, and perhaps others elsewhere in the body We should now inquire whether they are parallel or in series, and what their exact physical relationship is with the muscular, or other elements of the wall This will be a difficult question to solve in individual instances We are faced with a large group of cardiovascular reflexes I am sure we have not covered all the reflexes for which there is evidence of existence, but mainly those whose afferent nerves run in the vagi

I should like to speak about the reflex which has been described by Gruhzit and Moe (6,7) This is a very interesting investigation, but it is obvious that there are many more details to be worked out, as Dr Moe himself knows, it is not a criticism of his very important work He has shown that there is peripheral vasodilation in the hind leg I should like to know whether there is similar peripheral vasodilation elsewhere, whether it is accompanied by bradycardia or any change in breathing, and, whether this reflex fits into the

pattern of the other reflexes concerned in the central control of the circulation I mention this with some hesitation because I have been trying to think of experiments which could settle this point and I am quite sure that it is a very difficult thing to do

You will observe that evidence for the existence of this reflex was produced in an animal with the vagi cut and the carotid sinuses denervated Under those conditions the homeostatic reflexes as we generally know them have been removed and it may be therefore that the effects we see in their absence are greater than if they were present. Certainly the vasodilation produced was very considerable I think it remains to be seen to what extent this reflex fits into the pattern of the main reflexes controlling the circulation

The other reflexes with which we have been concerned aside from the reflex from the carotid sinus area have their afferent nerves in the vagi and this immediately poses a most interesting question The experiments of Professor Heymans (97) many years ago showed that when the carotid sinus nerves were cut the regulation of the circulation got out of hand and the blood pressure rose considerably At that time it seemed likely that we were dealing only with a reflex from the carotid sinus area and a reflex from the aortic arch It was a section of those two afferent reflex mechanisms alone which caused the rise of blood pressure

Now the situation is somewhat different Numbers 3 4 5 and 6 in Table IV are all reflex mechanisms for which some evidence exists I am not sure whether Numbers 3 and 4 might be identical and Numbers 5 and 6 also These four reflexes at least are de pressor reflexes and they have their afferent fibers in the vagi Thus I should like to suggest the possibility that these four reflexes from the heart and lungs which are distinct from the reflexes from the aortic arch may also play an important part in circulatory homeostasis However I do not know

So far as the reflexes from the atria are concerned I think it is clear that there are at least four possibilities I deliberately did not mention a fifth possibility that is that the atrial fibers might be concerned with some change in breathing We must always remember that the changes in the circulation and the respiration are very closely connected, and there is a hint in the literature at least that the atrial fibers might possibly be linked with some respiratory mechanism

On the right hand side of Table IV nothing has been said, I think about the ventricular receptors The evidence for their existence is not very good but they should have been mentioned

in connection with the coronary chemoreflex, and the Daly and Verney reflex and I am sorry I did not do so Whitteridge and Dickinson in their work present some indirect evidence that there are fibers in the vagus which fire during isometric contraction of the ventricular muscle It is possible that is related to the coronary chemoreflex and the Daly and Verney reflex

However the striking thing about the receptors on the right-hand side of Table IV is that they have all been discovered, as you know, by single fiber action potential records in the vagi They are, so far as we can tell fairly large fibers and I think we have evidence to suggest that there are other reflexes from the heart and lungs whose afferent nerve fibers are small

I think it is not generally acknowledged that there are limitations in the electrophysiological techniques which are available It is difficult to record action potentials from small fibers, and it may be as Zotterman has frequently pointed out that we are studying mainly large fiber action potentials which are easy to obtain, but perhaps not always very important The smaller fibers, which represent the lower half of the iceberg on which we are slithering about, have not been thoroughly investigated as yet

If we look at the reflexes from this point of view, another thought emerges I have suggested that they might be concerned in circulatory homeostasis However, there are two other possibilities first, we must consider the pain and nociceptive reflexes We know that strong stimulation of a large number of afferent nerves causes a fall of blood pressure and heart rate, and the existence of the reflex mechanisms of the heart and lungs might merely reflect the extension of the pain fiber system into those organs One then begins to wonder what their purpose is

The second possibility is suggested by the well-known observations on gills of fish Old experiments by McWilliam (98) demonstrated that mechanical stimulation of the gills of fish, and other parts of the eel's body, would easily cause a fall of blood pressure and heart rate Evidently this is a very ancient mechanism, and yet we do not know why it is there, we can only speculate Apparently we do not know enough about the physiology of fish

However, since the circulatory and nervous systems are based on that which was possessed by our primordial ancestors, perhaps there is a carry-over of these mechanisms in ourselves I do not think we should assume that every mechanism in the body has a useful purpose, there are many, such as the appendix, which are singularly useless and could be done without Perhaps some of the

reflexes from the heart and lungs fall into this category

I think we should preserve open minds on this subject We should recognize the possibility that these small fiber reflexes from the heart and lungs may be of importance in normal physiology as they very likely are in pathological physiology but we must wait for the future to show us their exact functions

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FUNCTIONAL PROPERTIES OF BLOOD VESSELS

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DR. COMROE REMARKED earlier that little was being said about the subject of shock and in the material which follows I see even less chance for any specific discussion of that topic Since my own studies* of the mechanical properties of the vascular bed evolved directly from the shock problem however it occurs to me that it might be of interest to this group to know of my personal orientation to this field

During the war many of us were worrying about what happened to the transfused blood in the animal or patient who died in shock in spite of significant transfusions As was evident in our previous discussion that problem still faces us I am one of those who have the conviction that at least some of that blood is lost within the vascular bed (1,2) In other words it disappears from the effective circulating blood volume but it is still somewhere within the vascular system That raises two questions First where is it? Secondly how does it get lost?

The problem of "where" is a difficult one to answer as indicated earlier in the discussion and is perhaps not the important question If we knew "how" it got there we should be in a position to resolve the mystery

In order to understand how blood could get lost in such a situation it was my feeling that we had to learn a great deal more about the physical properties of the vascular bed It was in this fashion that I became involved in an investigation of the mechanical properties of blood vessels These properties definitely important in

*The bulk of the work reported here was carried out in the Department of Physiology Western Reserve University Cleveland, Ohio and supported by a grant from the Cleveland Area Heart Society the most recent studies have been continued in the Department of Physiology Medical College of Georgia, Augusta, Georgia, with the support of the United States Public Health Service Portions of this work have been published previously as you will see from the references. I am indebted to Drs. J L Ankeney W S Edwards, A Hurlimann, and S M Sancetta for their able assistance in carrying out many of the experiments described here

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tem when we perform an injection to study the vascular distensibility

Except for these brief intervals of a few seconds when we momentarily cut off the normal blood flow to perform the injection we followed a rigid procedure of keeping the organ in communication with the circulation of the dog Thus although this is not a normal physiological preparation I think it is a little more physiological than some of the purely *in vitro* preparations that have been used

PRESSURE VOLUME RELATIONSHIPS IN THE AORTA

In order to comprehend the results which may be obtained with this method, let us start with the simplest system we could find by studying a single blood vessel We need a large blood vessel and therefore have selected the thoracic aorta The system we are dealing with in such a vessel can be visualized most easily if we consider first a two-dimensional picture In other words let us derive the tension and length relationships in the wall of the vessel In addition to our pressure-volume data this requires appropriate measurements of the dimensions of the aorta From these we may calculate from our injection records the changes in tension and circumferential length of the aortic segment under study choosing

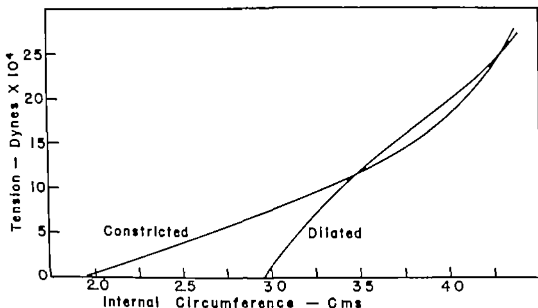


FIGURE 41 Tension-length diagrams for a segment of thoracic aorta before (*Dilated*) and after (*Constricted*) epinephrine calculated from data obtained by injection with blood at the rate of 50 cm³ per minute. Reprinted, by permission, from Alexander R S The influence of constrictor drugs on the distensibility of the splanchnic venous system, analyzed on the basis of an aortic model. *Circul Res* 2, *140 (1954)*

a consideration of circulatory homeostasis, and I suspect that some of the material we shall discuss will eventually be shown to have a specific pertinence to shock.

In approaching the mechanical and physical analysis of blood vessels, to which I should like to restrict our initial considerations, we immediately come upon technical difficulties in design of experiments. One is faced with the dilemma of conducting experiments under physiological conditions in which the data obtainable are extremely meager, or designing the experiment so as to obtain more valid data, which requires a radical departure from physiological conditions. That situation, of course, is encountered in other fields to some extent, but it is an especially difficult problem to resolve in this particular sphere of investigation. Were we to review the literature of this field, we should therefore need to concern ourselves with a critical survey of the many different techniques that have been brought to bear on the general problem.

To avoid such a lengthy discussion of different methodologies, I shall confine my discussion to the type of data which one can obtain with a single technique. Naturally, that happens to be the technique which I have employed. I should like to make it clear, however, that I do not present this method as necessarily the best technique for approaching any specific facet of the problem. I should also emphasize that many of the things which I wish to present here are in no way original, some of these phenomena were first described over 100 years ago (3). In spite of that fact, however, their fragmentary nature has resulted in their being neglected over the years.

Our technique uses three components: first, a motor-driven syringe that will permit us to inject known volumes of blood at a very constant and controllable rate (as we shall see, the rate of injection can be extremely important), secondly, a pressure recording system so that we can follow pressure changes within the blood vessels during the injection, and thirdly, an anesthetized dog which will provide us with an organ to submit to injection studies. In many of these studies we used morphine and sodium barbital as an anesthetic. When we were interested in reflex effects upon distensibility, however, we used chloralose with morphine.

Our procedure requires considerable surgical intervention. We must eliminate all collateral sources of blood loss from our injection site, and be prepared to interrupt, temporarily, the remaining channels of blood flow in order to have the system completely isolated and under the control of our injector and manometer sys-

Heymans Where does the epinephrine go according to your observations? Does it stay in the aorta or do you think it may be conducted by the circulation to other areas?

Alexander About a half a second after it is injected into the preparation and before it has had time to flow through and leave the aortic segment the circulation is cut off and it is trapped there

Heymans Does the interruption of the circulation behind the aorta, by clamping of the aorta not induce alterations in the circulatory system depending on the aorta which could interfere with the responses of the aorta after the circulation has been restored?

Alexander The criticisms you raise have considerable validity As I stated at the outset these are not physiological preparations I should give a few more technical details however

The aorta was permanently cannulated The cannulae at each end of the aortic segment were connected to large bore stopcocks and tubing from these stopcocks connected with the arterial and venous systems of the dog to provide for normal circulation of the segment Epinephrine was introduced through a side-arm in the arterial tubing and then the stopcock on the arterial side was closed. After three seconds for pressure equilibration the venous stopcock was closed and the motor-driven injector turned on

Heymans Therefore you did not touch the arterial wall by cutting off the circulation?

Alexander No

Dawes Were both ends of the aortic strip closed during the measurements?

Alexander Yes

Fremont Smith Therefore it was a static situation so far as blood flow was concerned?

Alexander That is correct there was no blood flow during the distensibility determination Some circulation to the posterior half of the animal was maintained, however by setting up a carotid to femoral shunt with large bore plastic tubing during the initial preparation.

This aortic segment was completely stripped all the intercostals had been tied, so it was denervated. We were dealing essentially with an isolated preparation In addition to that we carefully allowed an interval of ten minutes between each recording so that we had a period for stabilization before each injection.

That of course does not answer your criticisms At the moment I am not so much concerned about what is causing the changes

the circumferential dimension because it is the more significant one In our preparations, increase in volume due to elongation of the aorta accounts for only 20 per cent of the total volume increase, associated with a pressure change of from 0 to 250 mm Hg

Figure 41 shows two tension-length diagrams, one obtained from an aorta which was in a relatively dilated state, and the other from the same aorta after introducing epinephrine in the aortic segment These curves show, first, that we are dealing with an elastic system as the length increases, the tension increases Yet it is not an ideal Hookian elastic system, since the relationship is not rectilinear, but curvilinear, particularly in the case of the constricted curve The upper portions of these curves at high tensions (equivalent to pressures in the range of 250 mm Hg) exhibit a steep slope, indicating a relatively stiff system, at low tensions the slope is much more gradual, particularly in the constricted state, indicating a more distensible system

Such data are not new, they have been obtained by a number of workers One of the best studies of this phenomenon is that of Remington and his co-workers in the Georgia group (4), using different techniques but obtaining very similar results Their interpretation, which I think we should accept, is that at high pressures or tensions the elastic load is being carried by the fibrous tissue, which is the stiffest of the tissue components in the wall of the vessel As pressure is reduced from these high levels, the more distensible elastic fibers assume more of the load, and then at lower pressures progressively more of the load is carried by the smooth muscle, which is the most distensible, or the least stiff, of the components in the wall of the vessel In accordance with this interpretation, note that epinephrine has little action on the upper (fibrous) portion of the diagram, but greatly augments the manifestation of a more distensible element in the lower (muscular) portion

Knisely The human aorta does not have muscle except in the upper part (5)

Alexander The question of how much muscle there is in the aorta has been debated at length Distensibility studies give the impression that significant amounts of muscle are present in some aortic preparations, but not in others I think in this case epinephrine is acting on something I would use the epinephrine response as evidence that muscle was present

Heymans Is it a local application of epinephrine in the artery?

Alexander Yes

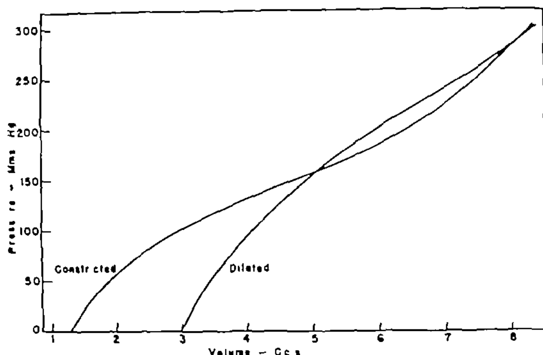


FIGURE 42. Retracing of the directly recorded pressure volume diagrams of the thoracic aorta that were used in deriving the data of Figure 41 Reprinted, by permission, from Alexander R. S The influence of constrictor drugs on the distensibility of the splanchnic venous system, analyzed on the basis of an aortic model. *Circul Res* 2, 140 (1954) *

with the data backwards Now let us restore the third dimension In Figure 42 we see the original data These are tracings of the original recordings transferred to the same abscissal scale Volume (which was equivalent to a time axis as we recorded it) is on the abscissa and the pressure recorded by our manometer is on the ordinate These curves in Figure 42 are the raw data from which the two-dimensional diagrams of Figure 41 were derived.

Comparing Figures 41 and 42 we see that the third dimension has altered the form of the curves particularly at the lower end even though the upper portions of the curves do not differ very much in form. More specifically the two dimensional diagrams approach the abscissa in somewhat of a parabolic fashion whereas the three dimensional diagrams assume a characteristic sigmoid twist particularly in the constricted vessel

The explanation of that inflection in the lower portion of the diagrams in Figure 42 which produces the sigmoid pattern resides in an old principle which was first clearly stated I believe by Laplace and more recently applied to the blood vessels (67) When we take an elastic sheet and convert it into a cylinder we

in terms of the whole animal's physiology, as what is changing in the blood vessel

Heymans That makes it clear that data obtained in these conditions may be quite different from those that would be observed if similar volume-pressure changes could be studied in the intact aorta

Alexander Definitely

Fremont-Smith The data obtained in any experiment are valid only in relation to the conditions under which they were observed, and one must be cautious about applying them to other situations

Heymans Dr Alexander started to say that he quite realized his conditions were very different from normal physiologic ones We have to keep that in mind when drawing conclusions from these experiments and observations

Green Was the tension in dynes?

Alexander It was dynes per longitudinal centimeter of aorta, which I related (in Figure 41) to centimeters of circumference To be strictly correct, these data should be expressed as dynes per square centimeter of aortic wall That forces us to assume homogeneity of the aortic wall, however, and I am not sure that we learn any more by doing that

Green Are you thinking of dynes that would tear the aortic wall in a longitudinal direction?

Alexander Yes, the tear would run longitudinally

Knisely Does this segment expand longitudinally?

Alexander Oh, yes

Knisely Thus, your dyne statement ought to have corrections for thickness of the wall

Alexander That correction has not been introduced, it is a small one

The data in Figure 41 are derived from records obtained with the motor-driven syringe At the moment the syringe is started, the pressure (or tension) has equilibrated at approximately zero The injection then proceeds at a rate of 50 cm^3 per minute, for a period of about eight seconds in this experiment During this period of continuous injection, continuous pressures within the vessel are simultaneously recorded which progressively ascend from zero to about 300 mm Hg

Burton That is slow enough so that the rate does not affect the pressure you obtain?

Alexander That is correct, at least, not significantly in the case of the aorta I purposely started off with the simpler two-dimensional diagram of Figure 41, even though it has forced us to deal

of Laplace I think what Dr Alexander has been discussing is a tension length diagram

Alexander There is one detail I might point out for its physiological interest Figures 41 and 42 tell us that the constricted vessel is more distensible over most of the pressure range This we have explained as due to a greater participation of the more distensible muscular element Thus contraction of the smooth muscle can effectively constrict the lumen of the aorta but at the same time it acts to increase aortic distensibility This relationship has been demonstrated by other techniques in the living animal (9) but the existence of this phenomenon has frequently been overlooked in our thinking

Nickerson Are you going to draw any conclusions regarding the serial or parallel arrangement of elastic and muscular elements from this diagram?

Alexander I would rather let someone like Dr Burton or Dr Lawton discuss that problem It is an important and intriguing question but it can become exceedingly complicated (10)

Knisely Dr Alexander this is not a criticism but I think it would be interesting to see if there were some musculature in each specimen Between what numbers was the segment?

Alexander It was between 2 or 3 and 6 or 7 in the dog I confess I have made no attempts to verify the existence of muscle histologically but the epinephrine does something If it does not work on the muscle I am curious as to what it is working on

Knisely On the connective tissue?

Burch Was there any volume change in the segment when epinephrine was applied?

Alexander That is shown in Figure 42 by the reduction in the initial volume at the zero pressure line

Burch Is that the volume of fluid injected?

Alexander This brings out one unique advantage of the aortic preparation Before we start the injection we may close the system off and then withdraw all of the blood within the aortic segment until complete collapse occurs After measuring the volume of the blood that has been taken out, it is returned to the aorta and then the injection with our motor-driven syringe is started. The initial volume measured in this fashion then becomes the point where we start plotting the curve when we retrace it on these abscissal units of total volume as seen in Figure 42

Green In obtaining the plots did you start at one end and move progressively to the other or did you start at one point and move back to another? Did you come back down the same curve?

introduce geometrical phenomena associated with the fact that the elastic tension is now acting tangentially to the wall of the cylinder The smaller the radius becomes, the more effective that tension will be in producing pressure within the vessel Therefore in Figure 42, as contrasted with Figure 41, there is a disproportionately steep rise in pressure in the lower pressure range where the radius of the aorta is relatively small It is this initial steep rise in pressure which is responsible for the sigmoid form of the diagram, an effect which is exaggerated when the vessel is constricted by epinephrine

Acheson As a pharmacologist, I am naturally interested in how much epinephrine you administered, and whether the time at which you gave it was important How long before the start of the infusion was it given? Did you obtain the same result at different levels of dosage?

Alexander We were looking for a maximal response that we would have no trouble in recognizing This is the response to a relatively massive dose of 20 μg, injected directly into the aortic segment I might add that we have used the regular Parke Davis product instead of the newer purified compounds Our interest is simply in defining what mechanical changes can take place in blood vessels, obviously this leaves much to be desired from a pharmacological point of view

Green I believe that the epinephrine Parke Davis have been producing for the last two years is practically the same as Winthrop Stearns' *l*-epinephrine, and is almost pure *l*-epinephrine, which contains less than 0 1 of 1 per cent of norepinephrine

Alexander I do not have the date of the preparation I used It was from the stock of drugs in Dr Wigger's laboratory, and quite possibly could have been in the laboratory at Cleveland when you were there, Dr Green

Green That is quite old, I left there December 1944

Lawton The S-shape of the curve does not necessarily follow from the Laplace principle There are any number of relationships that will lead to a similar S-shape Consideration of kinetics by Stacy (8), reported at Montreal, gave rise to a slightly S-shaped curve Some of the theories of rubber, and the elasticity of high polymers, give rise to an S-shape Thus, we have our choices as to what hypothesis we should like to use on the basis of S-shape

Burton I think Stacy was not talking about an S-shape in a tension-length diagram, but an S-shape in a volume-pressure diagram, and definitely there is no question how that rises We know that to translate it into a tension-length diagram, we use the law

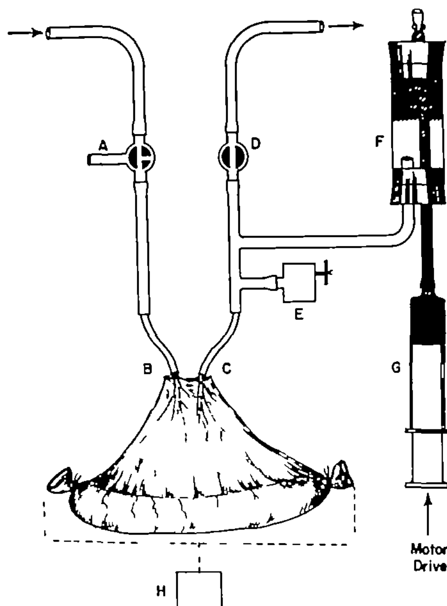


FIGURE 43 Diagram of the method employed for injecting the venous system of an intestinal loop Blood from the carotid artery of the dog flows through stopcock *A* and through arterial cannula *B* to the loop After perfusing the loop it flows out venous cannula *C* through stopcock *D* and then to the jugular vein. For distensibility determinations, stopcocks *A* and *D* are closed, and while recording venous pressure with manometer *E* injections are made through the oil trap *F* by the motor-driven syringe *G* Diagonal ruling indicates the portion of the system filled with mineral oil the remainder of the system is filled with the dog's own blood. In some experiments, changes in weight of the loop were measured by supporting the loop on the pan of the recording balance *H*

Alexander: Almost but not quite the same in the case of the aorta. I should like to turn to a consideration of these phenomena in the peripheral vascular bed, and in that case I shall have a lot to say about that particular problem.

PRESSURE-VOLUME RELATIONS OF THE VENOUS SYSTEM OF AN INTESTINAL LOOP

We recognize that the aorta is not an entirely typical blood vessel, but for the moment let us accept the relationships we have seen in Figures 11 and 12 as a prototype and see what other blood vessels look like. In approaching them, however, we have retained as closely as possible the same techniques of study except for the necessary surgical modifications. Specifically, let us apply these methods to the vascular bed of an intestinal loop, with a preparation set up in the manner illustrated schematically in Figure 13.

A loop of about 20 cm. of ileum is prepared with both ends tied off and all mesenteric branches except the main mesenteric artery and vein ligated. A connection is made between the carotid and the mesenteric arteries supplying the loop (*B*). This circuit passes through a stopcock (*A*) which permits us to cut off the arterial supply to the loop without any manipulation of the blood vessels; a side-arm on this stopcock also permits us to introduce drugs into the preparation. The mesenteric vein is cannulated (*C*), and the venous blood led through a second stopcock (*D*) and then to the jugular vein. This latter connection to the jugular vein consists of an open tube draining into a funnel, the pressure in the venous circuit when the stopcock (*D*) is open is determined by the hydrostatic level of this tube. Between the venous cannula (*C*), and the venous stopcock (*D*), there are take-offs for pressure recording (*E*), and for injecting blood with our motor-driven syringe (*F-G*). As a student of the Wiggers school, I still prefer a simple membrane manometer system with optical recording on photographic paper.

As outlined earlier, movement of the syringe (*G*) is accurately controlled by a heavy constant-speed motor drive, which actuates the syringe through a gear train providing for selection of different speeds of injection. To eliminate difficulties in manipulating a blood-filled syringe, smooth operation is assured by having the syringe itself filled with mineral oil, which communicates with the system through an oil-blood trap (*F*). In order to estimate the change in volume of the vascular bed of the loop produced by drugs, we transfer the loop to the scale pan of a strain-gauge balance (*H*), giving us a continuous electrical recording of the weight of the loop

Alexander Yes We had to treat these preparations with large doses of atropine to prevent intestinal motility which I might say is quite a technical problem. One advantage we discovered is obtained with the loop hanging on the scale pan of the balance This shows up intestinal motility fairly sensitively as undulations in the weight recording

Heymans I quite agree with you that atropine will rule out some of the intestinal motility but atropine does not rule out the action of epinephrine on all structures in the intestinal loop

Nickerson We are in an unfortunate situation pharmacologically in that I do not believe there is any procedure or agent which can effectively eliminate the effect of epinephrine on the intestinal smooth muscle

Alexander I realize that there is ground for criticism on this point and I have been pleading with the pharmacologists to provide me with a drug that would knock out the intestinal smooth muscle and not interfere with the vascular smooth muscle

Acheson I assume it is impossible to make these measurements in the absence of atropine Or does its absence merely make them less accurate?

Alexander It is quite possible to make these measurements without atropine provided one is fortunate On the infrequent occasions when in the absence of atropine an injection record can be completed without any evidence of intestinal motility appearing during the process the curves look just the same as those obtained in the atropinized preparation The more common experience in the absence of atropine however is to get part way through the injection and then find a peristaltic wave coming along which seriously distorts the pressure recording It is known that contraction of the smooth muscle of the intestine can quite effectively compress the blood vessels in that organ (11)

Heymans In addition to its action on the intestinal movements don t you think epinephrine could also act on some other structures in this loop and interfere with the responses obtained by injecting it into the artery? There are many influences I should say other than the action on the movements of the intestine which are produced by epinephrine Therefore this situation is a very complicated one and it may be that we are trying to solve a problem with many unknowns and variables

Stead I am just wondering as to veins in this preparation

Alexander Actually the pressure volume diagrams that we have recorded from the intestinal loop preparation are dominantly venous although I do not want to defend the point at this time

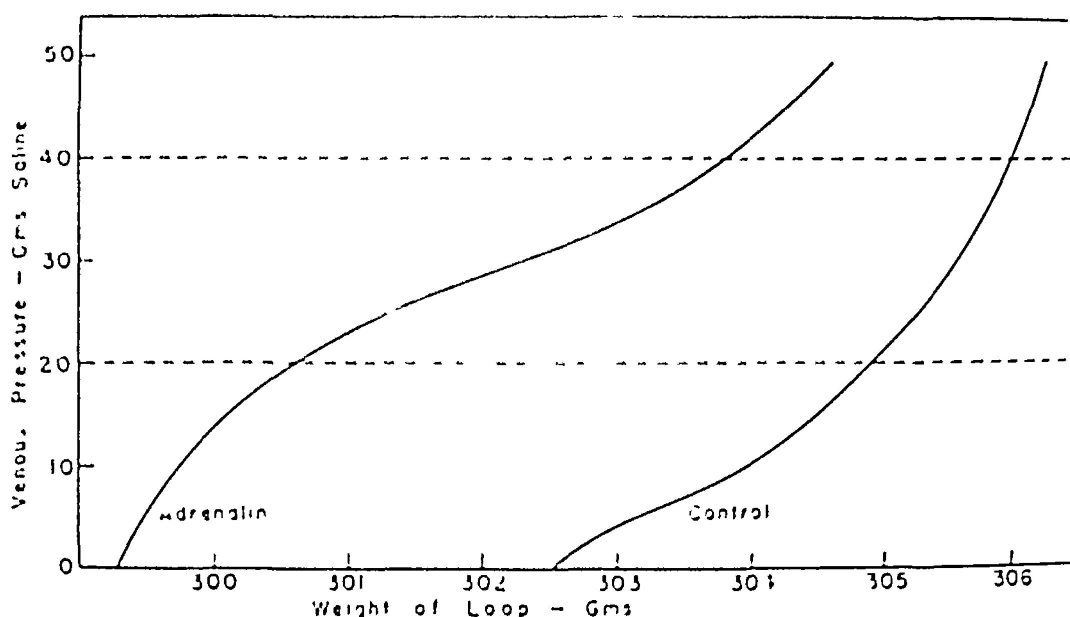


Figure 44. Pressure-volume (weight) diagrams obtained from an intestinal loop before and after epinephrine. Veins injected at the rate of 60 cm³ per minute. Reprinted by permission from Alexander, R. S.: The influence of constrictor drugs on the distensibility of the splanchnic venous system, analyzed on the basis of an aortic model. *Circul. Res. 2, 140 (1954).*

That is obviously not a very good quantitative method, but it permitted us to make some estimate of the changes in the vascular volume.

The type of information we obtain with this preparation is shown in Figure 44. After introducing the drugs into the side-arm of the arterial circuit supplying the loop, the arterial stopcock was closed. In the case of the intestine, it then required a period of ten seconds for venous drainage and pressure stabilization. The venous stopcock was then closed and the motor-driven syringe started. Figure 44 shows the venous pressures recorded, related in this case to the change in weight of the loop as recorded with the strain-gauge balance.

Heymans: Was the artery isolated from the surrounding tissues?

Alexander: Yes, it was completely denervated. Actually, in these experiments, the loop was grossly removed from the animal.

Heymans: Was the artery disconnected from all the surrounding tissues near the loop, or not?

Alexander: It was dissected free so that it could be sectioned and cannulated.

Heymans: Could any epinephrine from the artery get into the surrounding tissues?

Alexander Yes We had to treat these preparations with large doses of atropine to prevent intestinal motility which I might say is quite a technical problem One advantage we discovered is obtained with the loop hanging on the scale pan of the balance This shows up intestinal motility fairly sensitively as undulations in the weight recording

Heymans I quite agree with you that atropine will rule out some of the intestinal motility but atropine does not rule out the action of epinephrine on all structures in the intestinal loop

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Alexander Actually the pressure volume diagrams that we have recorded from the intestinal loop preparation are dominantly venous although I do not want to defend the point at this time

EDITOR'S NOTE Dr Alexander would like to add the following to his remarks at the conference

> I was here alluding to work initiated just before leaving the laboratory to attend the conference, which was completed shortly after returning to the laboratory If a pressure manometer is introduced into the arterial circuit through the side arm at A (Figure 13), injection of the mesenteric vein at the rates employed here fails to have any influence on the arterial pressure recording, even though the injection proceeds for ten seconds This is interpreted as evidence that retrograde flow to the arterial side of the vascular bed does not occur under the conditions of these experiments and therefore we are studying strictly splanchnic venous distensibilities (12)

Selkurt There is one other technical point, and that is the possibility of the translocation of fluid from the blood into the lumen in terms of filtration through the capillary bed This whole system is included, is it not?

Alexander That is right

Selkurt Does that in any way affect the experiment?

Kinsely Is the loop entirely amputated?

Alexander Yes The question Dr Selkurt raised is a very important one, on which we shall offer evidence in a few moments Briefly, if we reverse the syringe and withdraw all the injected fluid, we recover all the injected blood with only a slight deficit in pressure as compared with the initial pressure before we started the injection This decrease we interpret as leakage from the blood vessels we are studying, but the deficit is so slight that we do not believe that sufficient leakage occurs to distort, qualitatively, the form of the curves being obtained Obviously we would feel much happier if some of these technical imperfections in methodology, which you mention, could be eliminated, but we have not been able to solve completely the problems of experimental design

Acheson Do I understand that each curve represents one excursion of the syringe, and therefore changes with respect to time?

Alexander That is right

Acheson What I am thinking is that the epinephrine in this case is not going to have a steady state effect, but will also be changing with time

Alexander In this case we allow 15 seconds after intra-arterial administration of epinephrine for the system to stabilize We do not have a right to expect complete stability, but with massive doses of 20 μg of epinephrine injected directly into the artery supplying the loop, it is our opinion that a maximal plateau is reached so far as the constrictor effect is concerned, which lasts for many seconds

This inference is supported by such observations as the duration of the reduction in blood flow through the loop which one observes after such a dose of epinephrine

Acheson That is the same curve is obtained whether one waits for 10 or 15 seconds?

Alexander Yes.

Heymans Observations on the isolated carotid sinus and carotid artery preparations showed that at high internal pressure ranges leaks through the capillary bed (*vasa vasorum*) of the arterial wall occur These leaks may perhaps be closed by epinephrine Could that not have an influence on your data?

Alexander As I said in reference to Dr Selkurt s question the ability to recover the volume we inject offers no support for the idea that there is significant leakage even though there is evidence of some minor leakage as one would expect In all preparations in which we have used this injection technique we have never seen severe leakage except after toxic agents such as massive doses of histamine or sodium nitrite

Knisely How long do you wait between amputation and the time the injection is made? I raise that question because the longer the time the more chance there is for stagnant anoxia to occur

Alexander We preserve a normal circulation through the preparation at all times except for the brief interruptions to perform our injections After completing the surgery incident to the initial preparation we purposely wait for about two hours for complete control of leakage points resulting from the surgery as well as for stabilization of the preparation

Knisely For how long is the circulation cut off?

Alexander In the case of the intestinal loop the epinephrine is given about 5 seconds before the arterial flow to the loop is cut off We then wait 10 seconds for venous drainage followed by an interval of 3 seconds between closing the venous stopcock and starting the injection syringe At an injection rate of 60 cm³ per minute the injection takes another 5 to 6 seconds This represents a total interruption in blood flow of less than 20 seconds

Knisely There is not much time for disintegration of blood vessel walls

Alexander There is no suggestion of that

Howard As I understand it, you have a loop of bowel and are measuring the blood volume and venous pressure?

Alexander Yes

Howard During the time of infusion with no outflow?

Alexander That is right.

Green Did you say that the peristaltic wave changed the weight of the loop or the pressure?

Alexander It does both. Peristaltic activity compresses the mesenteric veins and thereby directly alters the venous pressure we are recording. In addition, since the loop on the scale pan is still connected with the cannulae and perfusion tubing, peristaltic activity introduces drag between the cannulae and the scale so as to alter the apparent weight of the preparation. This last, of course, is not a real weight change.

Heymans Before we can consider the conclusions we have to agree on the experimental conditions and ascertain whether there is leakage at certain pressure ranges in the artery. Our experiments have been performed on isolated segments of artery and under static pressure. As in the experiments of Lundgren (13) on the same preparation, we found that the leaks could be markedly decreased or even avoided by filling the closed arterial segment with a dextran solution. The large dextran molecules close the capillary bed of the arterial wall.

Alexander But I did not employ static pressures.

Nickerson I think there is a morphological explanation for these differences. Dr. Heymans' preparation was a completely stripped segment of a large artery, and the connections of the *vasa vasorum* with the rest of the vascular system were all sectioned, that is, he had an open-ended system. On the other hand, I suspect that in Dr. Alexander's preparation, to a large extent, the *vasa vasorum* were still connected with the rest of the vascular system. Fluid was probably still going through them, but the leakage was back into the system he was measuring, rather than into the muscle bath.

Green I think that is true with the intestinal preparation, but not with the isolated aorta.

Alexander I think that this leakage problem will be answered by the data we have, when they have been analyzed. As we have previously pointed out, the curves obtained from the aorta (Figure 42) were very similar to those which we found in the intestinal loop preparation (Figure 44). In both preparations sigmoid curves were observed, and in both instances the action of epinephrine displaced the curve to the left, particularly over the low pressure range, with an exaggeration of the sigmoid twist. This agreement between the results obtained from a very simple system, and from a system which is infinitely more complex, anatomically, gives us confidence for extending our interpretations. It is our basis for

suspecting that the numerous technical details which you have criticized are the sources of quantitative rather than qualitative errors

In the intestinal loop we again see a marked increase in the distensibility of the vessels produced by the constrictor drug over the pressure range of 20 to 40 cm of saline However the sigmoid twist is intensified by epinephrine to the point that at low pressures below 20 cm of saline the constricted curve tends to rise more steeply indicating a greater stiffness in the constricted vessels This again would appear to relate to the Laplacian phenomenon In a vascular bed containing much smaller vessels than the aorta a greater influence of the Laplacian effect is exactly what should be anticipated

If we could accept this picture of vascular distensibility as being dependent upon the elastic properties of the various components of the vessel wall as illustrated in Figure 41 complicated by the Laplacian effect which becomes progressively more important as we study smaller vessels then we would have a very sound basis for analyzing the distensibility of the vascular system Unfortunately it is not so simple as that

One complication which many of you have anticipated, is brought out in Figure 45 In this experiment we did not use any drugs the diagrams are of successive injections into the intestinal loop at rates of from 10 to 100 cm^3 per minute as indicated to the right of each curve The 10 cm^3 per minute injection required about 30 seconds that of 100 cm^3 per minute took 3 seconds In this case we recorded the pressure during the injections without any attempt to measure changes in initial volume the loop was not on the recording balance.

One immediately sees a major problem It explains why I have been emphasizing the use of a motor-driven syringe with continuous pressure recording The constancy of the rate at which the blood vessels are distended is extremely important if reproducible results are to be obtained It is evident in Figure 45 that a tenfold change in injection rate produces a tremendous difference in the pressure volume relationships that are measured.

Another way of demonstrating the time dependency of pressure volume relationships is to inject blood and then withdraw that same blood at exactly the same rate as shown in Figure 46 In this figure and in the following figures we finally have the evidence which we should have had some time ago it represents my answer to the leakage problem.

Alexander That is right

Green Did you say that the peristaltic wave changed the weight of the loop or the pressure?

Alexander It does both Peristaltic activity compresses the mesenteric veins and thereby directly alters the venous pressure we are recording In addition since the loop on the scale pan is still connected with the cannulae and perfusion tubing peristaltic activity introduces drag between the cannulae and the scale so as to alter the apparent weight of the preparation This last, of course, is not a real weight change

Heymans Before we can consider the conclusions we have to agree on the experimental conditions and ascertain whether there is leakage at certain pressure ranges in the artery Our experiments have been performed on isolated segments of artery, and under static pressure As in the experiments of Lundgren (13) on the same preparation we found that the leaks could be markedly decreased or even avoided by filling the closed arterial segment with a dextran solution The large dextran molecules close the capillary bed of the arterial wall

Alexander But I did not employ static pressures

Nickerson I think there is a morphological explanation for these differences Dr Heymans' preparation was a completely stripped segment of a large artery, and the connections of the *vasa vasorum* with the rest of the vascular system were all sectioned, that is, he had an open-ended system On the other hand, I suspect that in Dr Alexander's preparation, to a large extent, the *vasa vasorum* were still connected with the rest of the vascular system Fluid was probably still going through them, but the leakage was back into the system he was measuring, rather than into the muscle bath

Green I think that is true with the intestinal preparation, but not with the isolated aorta

Alexander I think that this leakage problem will be answered by the data we have, when they have been analyzed As we have previously pointed out, the curves obtained from the aorta (Figure 42) were very similar to those which we found in the intestinal loop preparation (Figure 44) In both preparations sigmoid curves were observed, and in both instances the action of epinephrine displaced the curve to the left, particularly over the low pressure range, with an exaggeration of the sigmoid twist This agreement between the results obtained from a very simple system, and from a system which is infinitely more complex, anatomically, gives us confidence for extending our interpretations It is our basis for

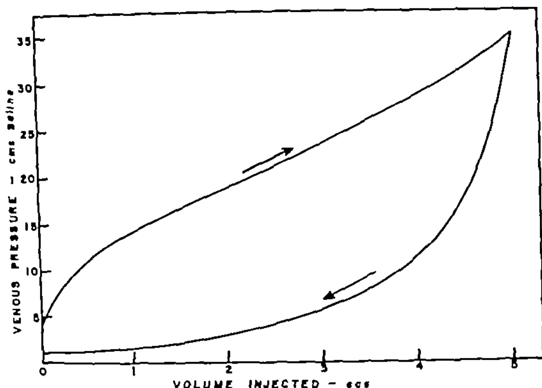


FIGURE 48 Pressure-volume diagrams obtained by the injection and immediate withdrawal of blood at the rate of 60 cm³ per minute from the mesenteric vein of an intestinal loop

typical one in this regard because the discrepancy at zero volume is greater than usual

Knisely Does the difference in space necessarily indicate volume difference? Might it be due to changes in the coefficient of elasticity of the smooth muscle during that time?

Alexander At a given pressure let us say at the 10 cm level there is a tremendous difference in volume Indeed in terms of the volume increment there is about a 1 000 per cent increase between the upcurve and the downcurve In the upcurve it is about a 0 4 ml. increment, whereas coming down it is about 4 ml Thus very large volume changes may be obtained in the vascular bed under the same pressure conditions depending upon the past history of pressure exposure of that vascular bed.

Green Are these venous pressures?

Alexander Venous pressure recorded from the intestinal loop

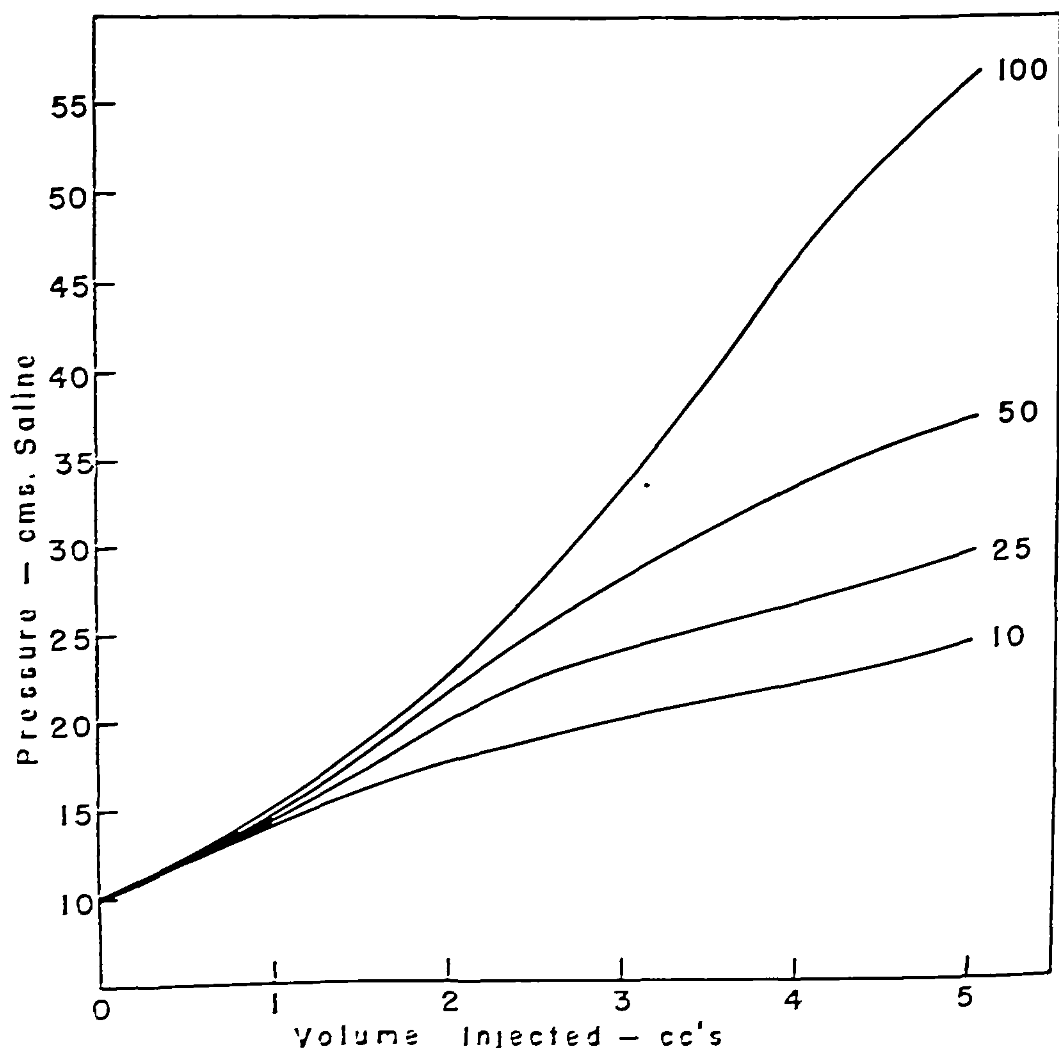
Bozler How rapidly was the injection made?

Alexander At a rate of 60 ml. per minute

Howard Was withdrawal made at the same rate?

Alexander Yes

The pressures recorded during injection are indicated by the upwardly directed arrow, at the peak, the gear train was reversed to withdraw the same blood at exactly the same rate You will note that at the point of "zero" volume, the two pressures are not quite the same To recover all the blood we injected, we lowered the pressure slightly below that at which we started This discrepancy can be attributed to leakage of the injected blood, but it is entirely too small to indicate that such leakage results in any gross distortion of the curves we are observing Actually this experiment is not a



[illegible]

As we would anticipate the second injection did not give us the same curve as the first Somewhat to our surprise however we found that the withdrawal curves were superimposed The original data of course were not points as suggested here but were continuous curves To transcribe the curves from the original photokymograph paper onto a common abscissal scale of volume we measured a series of points as indicated I think you will concede therefore that the slight variations between the open and the closed circles measured on the withdrawal curves are small enough to be within the error of such a measurement and that I am justified in saying that the curves are superimposed In describing this type of phenomenon we have a problem regarding terminology We are obviously dealing with a time-dependent effect This type of thing giving us a loop characteristic to our diagrams has frequently been termed "hysteresis" Recently many people have been objecting to the careless way in which hysteresis is being used in the biological sciences and have suggested that other terms should be introduced Some are now substituting the term "stress relaxation" for this type of behavior in biological phenomena. I believe Dr Richard Lawton is one proponent of that term and I have discussed it with him at great length

I understand that "stress relaxation" has been adopted by physicists working on rubber If we accept the idea that the aorta is like rubber the transfer of the term would be indicated. However I am not at all sure how closely the blood vessels duplicate the situation in rubber particularly in respect to these loops seen in Figures 46 and 47 Therefore at present I prefer to call this phenomenon in blood vessels a "delayed compliance"

Burton As a physicist, I do not think it is correct to use "hysteresis" in connection with time-dependent things It is correctly used in connection with what you would call "history-dependent" things In other words it is not the time you take to magnetize or demagnetize a magnet, (the first use of the term "hysteresis") that matters it is whether it has been magnetized or demagnetized.

Comroe Is the return loop not hysteresis?

Burton I think this looping depends upon the fact that the vessel has been stretched rather than relaxed. You could call it hysteresis but in so far as it depends on the rate that it is injected and at which it is withdrawn it is not hysteresis This is a "time-dependent" loop

Burch Don t you think hysteresis is playing a part?

Lawton According to my understanding of "hysteresis" a gen

Howard I do not understand your curve Were 4 ml going in, or were they already in? The pressures are equal

Alexander That, of course, is a very difficult question, I hope we have the answer

STRESS RELAXATION, HYSTERESIS, DELAYED COMPLIANCE

Burch Does the shape of the return graph vary a great deal?

Alexander Figure 47 will answer your question, Dr Burch As you will see, we have introduced another variation Again we have an intestinal loop injected at the rate of 60 cm³ per minute

Curve No 1 represents the initial injection following ten minutes for stabilization of conditions within the loop Curve No 2, as indicated by the solid circles, represents the injection which was performed immediately after completing withdrawal of the first injection Thus, it went in, out, in, and out

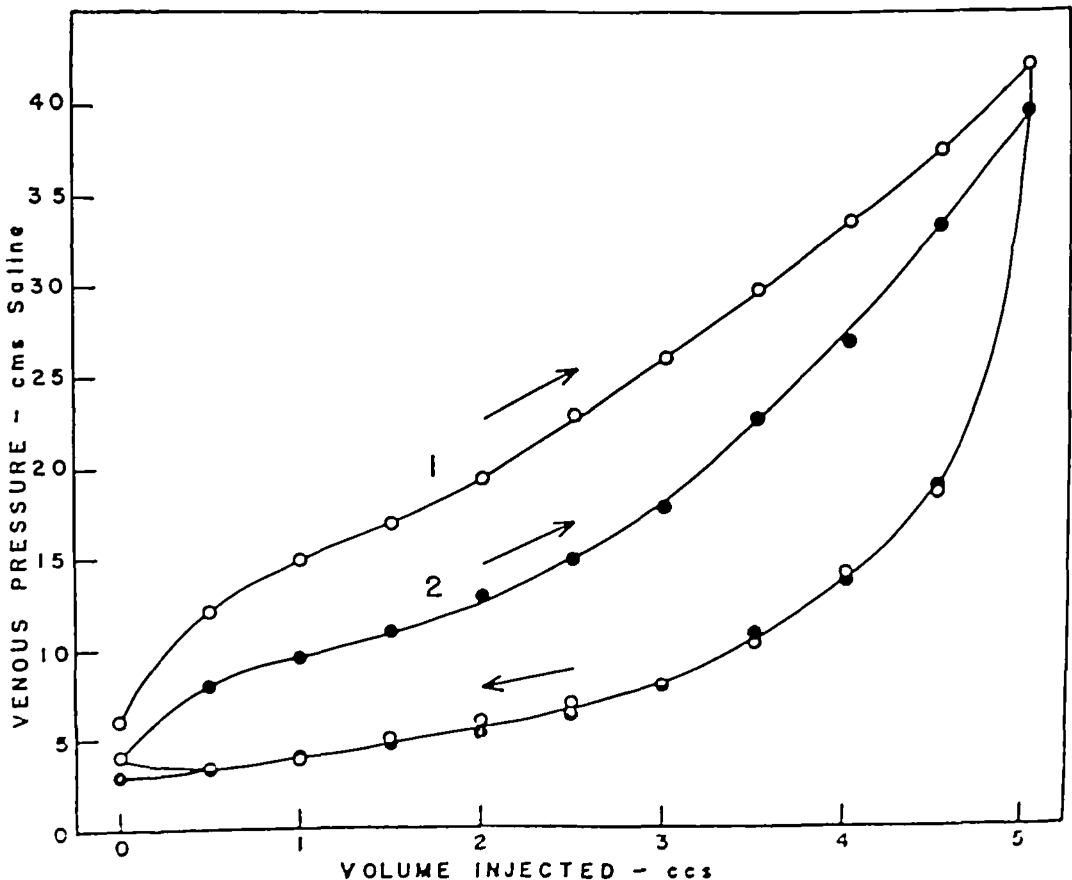


FIGURE 47 Pressure-volume diagrams as in Figure 46, except that a second cycle of injection and withdrawal was repeated immediately after the first Reprinted by permission, from Alexander, R S Edwards W S, and Ankeney J L The distensibility characteristics of the portal vascular bed *Circul Res* 1, 271 (1953)

superimposition of the withdrawal curves observed in Figure 47 This relationship does not fit with many of the hypotheses which might be advanced to explain the looping characteristic Many processes (e g viscous drag) should give concentric loops which move towards or away from a medium trend Here obviously the injection curve is moving but the withdrawal curve is not moving

Burton I do not understand your conception of a concentric loop

Alexander By concentric loops I imply a system of loops in which the ascending and descending curves bow to either side of a mean pathway Any process increasing the degree of bowing on the ascending pathway should produce a similar increase in bowing of the descending pathway in the opposite direction so as to preserve the relative symmetry of the loop about a fixed mean

Richardson Is this the same sort of thing that many people speak of in physiology and pharmacology as "the physiological state"?

Alexander I do not use that term I am not quite sure how you have used it. Therefore I cannot answer that

Richardson Suppose you do this ten times Do you get to the point where the withdrawal and the injection are the same?

Alexander We approach it but in no sense do we get there

Dawes You mean if you do the third then it falls below the second?

Alexander Yes but it is much closer to the second and we have never been able to get down to the withdrawal curve

Knisely And all withdrawal curves are constant?

Alexander If we use the same rate of withdrawal

Richardson In other words you are approaching constant conditions?

Alexander Yes in a dynamic sense

Dawes If you then wait for 5 minutes and repeat the process do you obtain the same initial curve?

Alexander We are back on Curve No 1 We have waited 10 minutes as a rule although in 5 minutes we are pretty close to it

Let us raise one further question now I think we have established that there is a time-dependent feature here Is it pressure dependent? That is important because this might be simple viscous drag which should be independent of pressure *per se* even though the superimposition of the withdrawal curves would argue against that. However it is significant to find out whether pressure has any influence on the type of behavior we see

Figure 48 shows another variation of these experiments We started out by making a typical injection and withdrawal of blood.

eral definition for mechanical systems is that it concerns the path (14) the path going up is different from the path coming down A number of reasons could be proposed for this, the chief of which is time Frequently there is a change in the temperature as the system is distended Thus, as Dr Burton says, there is a different system at the top from that at the bottom It is a warmer system, and it will come back along a different path Hence, mechanical and thermal changes are two possible causes of hysteresis

A third would be a change in the chemical structure of the system a phase change That is, if one thinks of this as a polymer system in which one is breaking cross bonds as it is stretched, the reformation of the cross bonds may take place at a different rate on the return from that of the breaking process going up This would give rise to a loop. Rubber goes through a process of crystallization when it stretches, and the decrystallization process takes place at a different rate from that of the crystallization process One, therefore, gets a loop arrangement Thus, there are, to my mind, many different causes for hysteresis, and one has to seek to eliminate them as best one can

Alexander I shall call this "delayed compliance" until I am sure what it is I think that would be the time to settle the semantic difficulty

Burton The word "compliance" disturbs me I cannot remember the references, but I have just read a paper in the field of elasticity in which the word "compliance" was used as meaning something quite different This, I think, is a very serious thing, let us correct this source of confusion before it starts

Knisely There is an excellent glossary of rheological terminology called *Industrial Rheology and Rheological Structures*, by H Green (15) Furthermore, it provides an excellent simple introduction to many rheological concepts currently in use

Lawton Dr Alexander and I have been through this problem of terminology in correspondence I have tentatively come to the conclusion, after talking with a number of people, that perhaps the term "delayed compliance" is not too bad To be sure, "compliance" is used in an entirely different manner, but one can use "delayed compliance" provided one explains how one is using it

Knisely You cannot select a word until what is happening has been interpreted

Alexander That is right Proceeding, then, with that idea, what is happening?

One further point should be brought out in reference to the

superimposition of the withdrawal curves observed in Figure 47 This relationship does not fit with many of the hypotheses which might be advanced to explain the looping characteristic Many processes (e g viscous drag) should give concentric loops which move towards or away from a median trend Here obviously the injection curve is moving but the withdrawal curve is not moving

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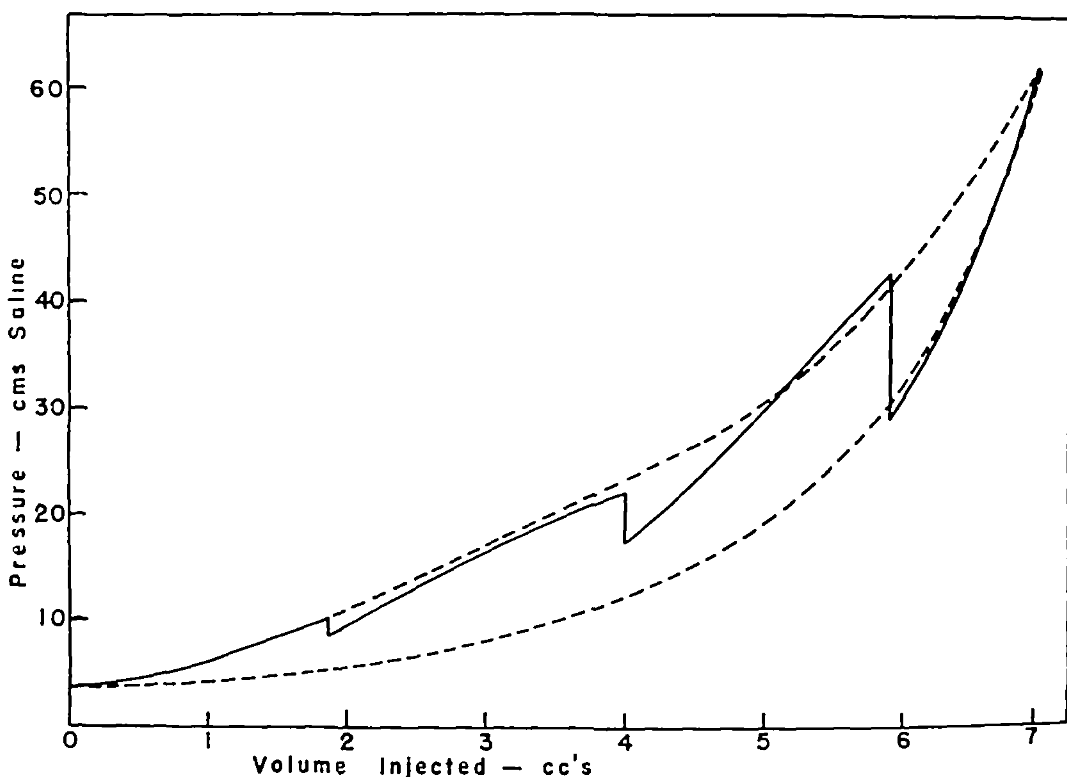


FIGURE 48 Comparison of a continuous injection and withdrawal (dashed curves) with an injection at the same rate, but interrupted at three points for intervals of 10 seconds

In this case we used an injection and withdrawal rate of 37 5 cm^3 per minute As indicated by the dashed curves, this gave us a loop which was not as wide as we have seen before at faster injection rates, but nevertheless a loop was still present Then we repeated the injection at the same rate, but interrupted it periodically, producing the curve shown by the solid line of Figure 48 The three vertical notches represent three interruptions in the injection process, each of which indicates a stoppage of the injecting syringe for a period of 10 seconds These 10-second interruptions were in excess of the total time required for the initial continuous injection (upper dashed curve)

Note the first interruption We obtained a very small fall in pressure, even though we had static conditions for ten seconds We did not in any sense get down to the withdrawal curve

With the second interruption we see a somewhat greater fall We were still not down to the withdrawal curve, although we were obtaining a steeper slope When we reach our third interruption point, the pressure level rose significantly When the interruption

is made under these conditions the pressure falls down sharply to the withdrawal curve This figure demonstrates that the difference between the injection and the withdrawal curves is not merely a matter of time High pressures must be created within the vessels in order to produce the shift from the injection distensibility pattern to the withdrawal distensibility pattern

Dauces This is still intestinal loop?

Alexander Yes

Fremont Smith What happens to the withdrawal curve at the end of the experiment

Alexander A withdrawal curve at the end is essentially the same as that observed after the initial injection

Heymans When you say "withdrawal" that means interruption of blood flow at the same time?

Alexander Blood flow through the preparation is cut off during each injection representing about 20 seconds for the continuous injection and 50 seconds for the interrupted injection

Heymans When you interrupt blood flow you are not only changing pressure but also alterations in oxygen supply and CO withdrawal. Thus there are other factors besides pressure change in your experiments

Green What was the time required for the third drop?

Alexander Ten seconds Each interruption was 10 seconds

Green How quickly did it take to get to the bottom did it take the full 10 seconds?

Alexander It resembles a logarithmic curve which is pretty well plateaued at the end of 10 seconds We have not analyzed it quantitatively

Comroe Does leakage through the capillary bed play any role when the pressure in the system exceeds from 25 to 30 mm of mercury?

Alexander It probably plays some role

Comroe But that would explain only a small part of it?

Alexander I think so

Lawton At the first interruption would the pressure continue to decay if sufficient time were allowed?

Alexander We have not done that, because if we continue stagnant conditions too long we eventually see definite evidence of reactive hyperemia As Dr Heymans pointed out a moment ago that would complicate the story

Lawton This would suggest that different elements are participating at the lower from those at the higher end of the curve

Alexander That could be

Knisely What do you mean by reactive hyperemia, does the whole thing fill up and turn red?

Alexander No, what I mean by that is this as one keeps these preparations stagnant over periods of 20 to 30 seconds, one starts to find a drop in pressure with no change in volume injected, which would imply that the blood vessel is opening up

Fremont-Smith Vasodilation?

Alexander Yes, vasodilation associated with stagnation of the circulation

Now let us see if we can answer the fundamental question which is confronting us What is responsible for this delayed compliance? Many possibilities could be considered, but perhaps the most obvious factor is the vascular smooth muscle, what is happening to that?

Actually we have performed over 100 individual experiments which suggest that the smooth muscle holds the key to the situa-

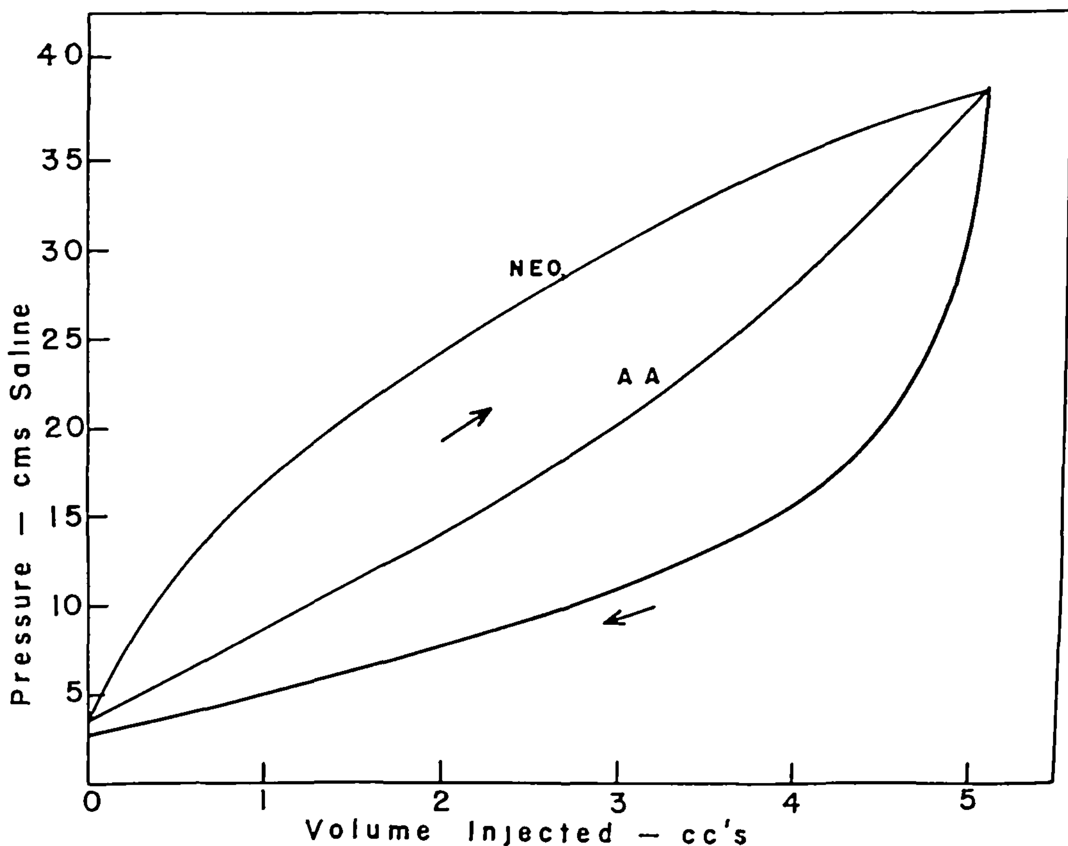


FIGURE 49 Injection and withdrawal pressure-volume diagrams from an intestinal loop following neosynephrine (*NEO*) and adenylic acid (*A A*) Reprinted, by permission, from Alexander, R S The source of delayed compliance in the vascular bed *Circul Res* 2, *183 (1954)*

tion. One particularly fortunate experiment shown in Figure 49 however seems to demonstrate it rather neatly This is a typical pair of injection withdrawal curves except that before the initial *injection we administered neosynephrine to constrict the vessels* After completing this injection and withdrawal recording we allowed the usual interval of 10 minutes for restabilization of the *blood vessels then dilated them with adenylic acid* and repeated the injection and withdrawal As would be anticipated the con stricted curve differs significantly from the dilated curve obtained *during the two injections* The lucky coincidence in this particular experiment resides in the fact that the pressure volume peak reached in the two cases at the point of reversal of the injecting syringe happened to be almost identical This facilitated the demon stration that the two withdrawal curves were superimposable there was absolutely no measureable difference between the withdrawal curve following the constrictor drug and that following the dilator drug

My interpretation of this experiment is that during the injections the smooth muscle contributes to the elastic properties of the blood vessels Hence drugs which act on the smooth muscle can alter the form of the injection curve significantly On withdrawal how ever the failure of drugs to alter the curve would indicate that the smooth muscle has dropped out of the picture After the stretch ing of the vessels associated with the injections there is no longer evidence on withdrawal that the smooth muscle is contributing to the elastic properties of the blood vessels

In a sense this observation is not new physiologists have been observing this behavior in smooth muscle for many years As we load a smooth muscular organ, the smooth muscle tends to "yield" or "flow" so that if we maintain significant pressure for any length of time the smooth muscle elongates The elastic load is thereby passed over to the noncontractile elements in the system and we have essentially negated the action of the smooth muscle under these conditions

The physiological implications of this characteristic seem to be rather far reaching The typical smooth muscular visceral organ is described as a system which can adapt to changes in volume with minimal changes in pressure by this type of behavior Most of us have been reluctant to think that the vascular bed could adapt itself to changes in volume by such a mechanism without the participa tion of specific vascular reflexes Here in a completely denervated preparation however we observe the type of adaptive change

which is characteristic of smooth muscle For example, compare the behavior illustrated in Figure 48 with that observed in the denervated human bladder (16)

Bozler. If we allow a contracted muscle to shorten, tension drops, but rises again gradually Assuming a tonic contraction in the smooth muscle of the vascular bed, we can understand readily why, on the downward slope, the contribution of the muscle to the pressure temporarily drops out The magnitude of this effect, of course, depends on the strength of the tonic contraction Is there any evidence concerning this strength?

Alexander Only in the difference between the neosynephrine curve and the adenylic acid curve

Moe I should like to know how dependent this would be on time, the speed of injection Have you done it at different speeds under this kind of condition, once with neosynephrine and once with adenylic acid?

Alexander We have done it with different speeds There is slight evidence of a viscoelastic effect

Moe What I am thinking of is this Your withdrawal curves are always superimposable Presumably, if you injected slowly enough, you would retrace the withdrawal curve, wouldn't you, in the normal state?

Alexander: Theoretically, one should be able to do that except that it would require an extremely slow injection I think Dr Stacy (8) has been doing this type of thing by stretching the umbilical artery, which is a highly muscular artery His stretches are extremely slow I think he does approach the withdrawal curve

Lawton His observation was that the stress decayed away to zero in the umbilical artery If a sudden pressure is put on it and allowed to stay there, it will gradually, and almost completely, disappear

Burton Dr Lysle Peterson is doing similar experiments on the aorta (17)

It is really basic in physics that one has to think about the equation of motion of a sample of water or blood I shall put it in general terms The force on the syringe is one side of the equation It is equated to the sum of three terms The first of these is an "inertia" factor That is, it is something proportional to the mass moved and to the acceleration That is a Newtonian force (Isaac and the apple) The second term can be called a "viscous force," a force which is some function of the velocity, rather than of the acceleration Then, at the end of this equation, there is the third

term which we may call the "elastic force" which is some function of the displacement of the particle (or of the wall in this case) This force depends upon how stretched the wall may be The elastic force depends upon the amount of displacement i e the distension of the wall.

What Dr Peterson emphasizes is that we have no business in interpreting the force in such experiments as Dr Alexander is doing without considering all its components One has to go further and think "Which of these forces does the manometer interpret?" As you know it depends upon which way we insert the manometer catheter as in the Pitot tube We have no right to interpret our measurements without considering how much may be coming from the inertia or acceleration factors We have no right to interpret results as to how they depend on the elastic factor unless we subtract inertia forces I think that is the fundamental thing that has to be looked into in the interpretation of your experiments Dr Alexander When you suddenly push in fluid, you obtain a sudden rise of pressure and then a fall How much of this is an inertial component of force which has nothing to do with the elastic properties of the wall? How much of this is an acceleration transient?

Alexander Your point is well taken I have omitted these details from my discussion merely for the purposes of simplification Actually the records we obtained show quite clearly the phenomena which have been described by Dr Peterson as illustrated by an original recording shown in Figure 50 At the moment the injection is started, there is a transient upward fling of the pressure tracing (X) This initial transient I believe relates to the acceleration forces required to overcome the inertia of injecting blood into a stagnant system In addition there tends to be an over all upward displacement of the curve during injection which can be measured quantitatively by the displacement in the pressure recording which is evident at the start and stop of the injection (Y Y) I have spent considerable time debating the significance of this latter phenomenon with Dr Peterson it obviously reflects some force created near the tip of the injection cannula incident to the injection process but I am not certain that we agree on the exact physical conditions which are responsible

In any case we have subtracted these effects from the pressure curves in retracing them, so that they have been eliminated from the curves that I have shown you in the preceding figures It should be noted that the withdrawal curves exhibit the same phenomena acting in the opposite direction. I am not sure whether Dr Peterson

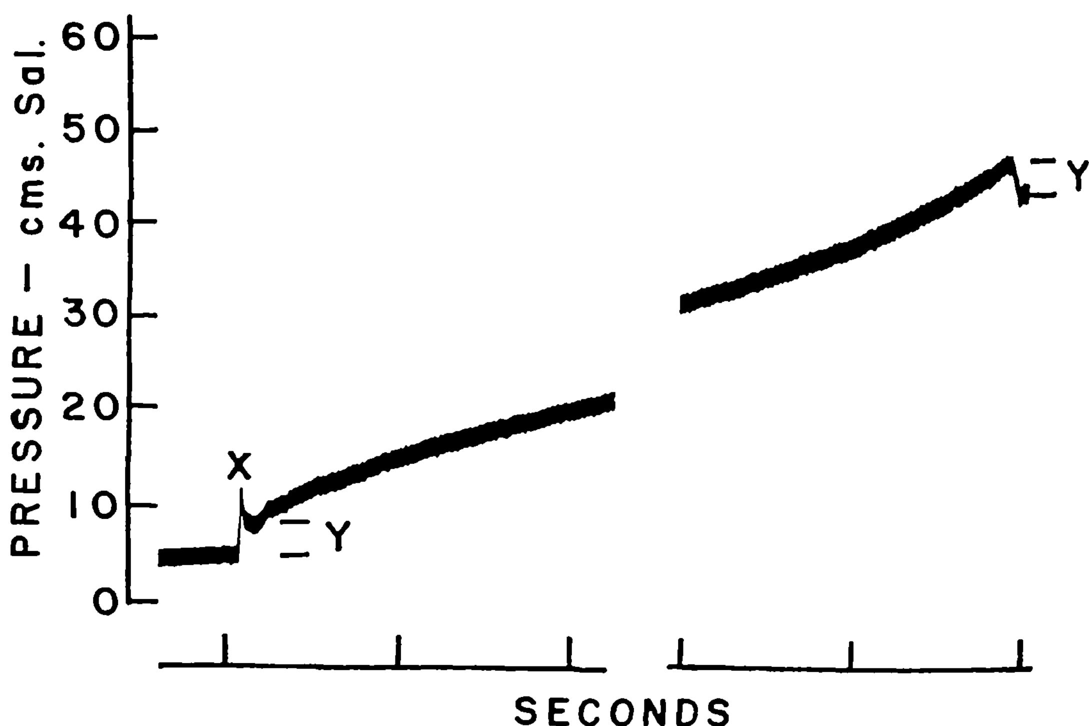


FIGURE 50 Segments of an original recording showing pressure phenomena at the start and the stop of an injection The *X* and *Y* components shown here have been subtracted from the recorded pressures in reproducing the curves shown in the other figures

would accept such an erasure of these phenomena from our curves, but it seems to me that these acceleration forces are not relevant to our primary concern of defining the elastic behavior of the blood vessels

Green I find it difficult to conceive of an inertia force lasting throughout that curve Once we obtain steady flow, the inertia force becomes zero, and we are dealing entirely with viscous or frictional forces, or with pressure losses due to turbulence

Burch What is the percentage of volume change in the intervascular bed?

Alexander We should like to know, but have been discouraged so far from trying to find out We have talked to various investigators to ascertain whether we might obtain an estimate of the blood volume in the loop Of course, I assume it is a small increment of the initial blood volume We still hope we can gather enough courage to try it

Burch Would you guess it to be in the order of 100 ml or 50 ml ?

Alexander I should say 50 ml

Burch A ten per cent change?

Alexander Yes.

Knisely If you wish to know the blood volume why not wash out the vessel system and see how many red cells you obtain?

Alexander That is the approach we are now considering I am planning to discuss with Dr Philip Dow the possibility of obtaining a washout method for that experiment

Burton Why couldn t you include some dye in the material to be injected and see how much it is diluted?

Alexander I think the mixing problem would be extremely difficult. I believe that a washout procedure would be better than the dye method

Burton It is washed out and then mixed up?

Alexander If a washout method is to be used you already have a dye Hemoglobin is present and it seems to me to be satisfactory

Knisely On the chance that the red cells are axial you might want to put in both red cells and dye

Alexander There are many problems arising from that approach

Burch I should like to point out an important application which this has to the plethysmographic method of measuring blood flow In this method the venous outflow is obstructed and the blood flowing into the part is recorded It is assumed that there has been no disturbance in hemodynamic phenomena when measuring the inflow For an objective test of this assumption it is important to study the venous and arterial sides simultaneously as is being done by Dr Alexander

Alexander I am very glad you brought that point up Dr Burch I think there are many fields in which this has to be reckoned with For instance evidence of adaptive changes in the venous system are frequently attributed to venomotor reflexes (18) In some situations it may be a simpler mechanism than that. Reflexes are certainly not acting in our preparations because they are denervated

Shorr If you were to interrupt the injection at the time when the smooth muscle was largely responsible for the change would you obtain a return that differed in its characteristics from one in which you increased the stretch beyond the range of smooth muscle and into that of the elastic fibers?

Alexander Yes you would.

Fine How did you denervate the loop?

Alexander In the intestinal loop everything was sectioned surgically

Fine You did not section the vessels of course?

Alexander The vessels were sectioned in the process of cannulation

Fine The entire root of the mesentery, too?

Alexander Yes

Fine You are quite sure you get rid of the fibers? I have dealt with that technique, and I think one cannot be really certain of that

Alexander Actually, these preparations are separated from the dog by a plastic tube

Fine The whole thing?

Alexander Yes

Fine Where does it lie?

Alexander It is either exteriorized, or it is transferred to the scale pan of the recording balance

Burch What is the appearance of the vessels of the intestines?

Alexander The gut remains pink and appears to be in excellent condition, provided that an excessive number of massive doses of drugs have not been introduced, and provided one avoids any maintained high pressure in the venous system of the bed To my surprise, a dog under the conditions of these experiments does not shock I anticipated having trouble with shock in the case of the intestinal loop, but the dog will maintain its blood pressure very nicely in spite of sodium barbital, an anesthetic some of you do not like

Heymans During your presentation you have frequently used the term "denervated preparation" I was talking about it with Dr Richardson, and he made the suggestion, which I think is a good one, that you use the term "decentralized" preparation instead, because there are many nerves left in the preparation

Alexander A very good point! I certainly concede to it

FACTORS THAT MAY AFFECT THE PRESSURE-VOLUME RELATIONS IN INTESTINAL CIRCULATION

A POSSIBLE ARTERIOVENOUS SHUNTS

Heymans I have been interested in arteriovenous shunts, also in the intestinal circulation, and I should like to know about the possibility of interferences from the opening and closing of these shunts in the intestinal loop, related to pressure and drugs I think that pressure and drugs, mainly epinephrine, may have an influence on shunting blood from the arterial to the venous side, because these shunts open or close down In your opinion, what influence does this factor have with your preparation? In other words, I

should like to know the role of arteriovenous shunts in your experimental conditions

Alexander At the outset of this study we were keenly interested to see whether we could learn something about arteriovenous shunts but we have yet to find any data which would give us definite information We should like to be able to dissect arteriovenous shunting from other phenomena occurring in the bed

Heymans If we look at the work of Masson (19) on arteriovenous anastomoses we shall find that there is a large amount of evidence for the presence of arteriovenous shunts We observed that shunts shift the blood from the artery to the vein without its going through the periphery under quite a good many conditions Thus because they are anatomically present and react under some conditions I believe they could play a role in the circulation of the intestinal loop

Alexander I am quite aware of that problem and I think Dr Zweifach could expand on that The vascular architecture here is being grossly neglected.

Burton May I challenge that statement? There are some beautiful studies in the literature by Barlow (20) on this vascular architecture

Alexander It has been grossly neglected in my experiments

Shorr Is it necessary in your study? All you need to do is distribute the pressure rapidly

Alexander No however I think the question of vascular architecture (21) is eventually going to be very important

Knisely Arteriovenous anastomoses (22,23,24,25,26,27,28,29 30 31) have been seen in numbers of different organs Probably they do not exist in every tissue and organ There have been very few direct measurements made of the diameters of arteriovenous anastomoses per unit volume of tissue in individual organs

B DECENTRALIZATION

Dawes The local nervous reflex has been mentioned. It is always much better of course to cut nerves rather than to use pharmacological tools indiscriminately

Alexander In other connections we used local anesthetics principally to test the effect of local traumatic effects associated with our surgery and we found that local anesthesia did not alter the picture we obtained. However beyond that I do not have anything to add The more recent work I have been doing has been carried out in preparations in which the nerves have been kept intact so that we could study the influence of vascular reflexes on these distensibility phenomena

Burton In our laboratory because we are biophysicists we have

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Fine The entire root of the mesentery, too?

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Heymans I have been interested in arteriovenous shunts, also in the intestinal circulation, and I should like to know about the possibility of interferences from the opening and closing of these shunts in the intestinal loop, related to pressure and drugs I think that pressure and drugs, mainly epinephrine, may have an influence on shunting blood from the arterial to the venous side, because these shunts open or close down In your opinion, what influence does this factor have with your preparation? In other words, I

group That was whether by halting the injection at the time when the curve represents largely the effects on smooth muscle the return curve has other characteristics than those exhibited when you push beyond the smooth muscle onto the elastic tissue

Alexander It is difficult to know exactly how to quantitate that for a precise answer By inspection it looks as though some of the delayed compliance effect had taken place In other words there has been some pushing over towards the relaxation curve one would obtain at high pressure However as indicated in Figure 18 it takes a fairly high pressure to push it over to what looks like an elastic tissue curve without muscle

Green Did you do any stepwise withdrawals as you did the stepwise injections?

Alexander We have not interrupted the withdrawal period That is an interesting phase which we have not taken up

Green Is there any difference in the rate of equilibration of arterial and venous pressure in the epinephrine-treated preparations as compared with one not so treated?

Alexander That would be an interesting thing to study

Green That might give an answer to the arteriovenous shunt question Dr Heymans raised.

Alexander Yes there is much more to be learned in that direction

Shorr Will Dr Alexander now recapitulate He might wish to consider the various objections that have been raised so that he may evaluate the relation of those modifying factors to the objective of his study

Alexander I shall be glad to attempt that. Since we have been discussing a new technique whose validity has not been established I am necessarily on the defensive My immediate concern is to acquire a tool for studying the distensibility characteristics of the vascular bed particularly the venous portion It is my feeling that such a tool is evolving and it is my hope that further developments will permit us to eliminate many of the justifiable grounds for criticism which you have raised.

The major point that we have attempted to establish in our injection studies into the venous system of the intestinal loop is that the elastic properties of these vessels are both time-dependent and pressure dependent This emphasizes the need of employing rigidly controlled techniques if we wish to compare the distensibility of peripheral vessels under different conditions

Apparently this markedly time-dependent and pressure-dependent elastic characteristic, which we have been calling delayed com

a habit of working on very unphysiological preparations such as the isolated perfused rabbit ear, and we have made it a rule concerning the interpretation of the peculiarities we see, that before we begin postulating that these are reflexes or myogenic effects, we do a control experiment by perfusing with cyanide. Very often one discovers that the same peculiarities are still there with very dead smooth muscle. I think that is a useful procedure.

Incidentally, the muscle is not dead right after perfusion with cyanide, it has to be worked a little. The metabolic block is farther back than the actual contraction of the muscle. After working the muscle with epinephrine once or twice, it is perfectly dead.

Alexander We have done very few experiments with cyanide because, once the observations on the effect of cyanide are completed, there is nothing further to do. I have been reluctant to terminate the experiment.

Lawton May I ask what provisions were taken against evaporation?

Alexander The intestinal loop was always packed with saline-soaked gauze.

Lawton Did you notice evaporation from the gauze? I mean, was there a drift in the scale pan weight?

Alexander There was some drift, but it was in the other direction, and was attributable to intestinal secretions which gradually accumulate in the loop during the experiment.

Bozler I should like to comment on the time factor in the hysteresis phenomena under discussion. It is not brought out in the hysteresis loops. I wonder if it might be valuable to study stress relaxation, which means injecting into the loop a certain volume of fluid, and then determining the decay of pressure. From corresponding experiments on smooth muscle, we know that the tension produced by stretching, slowly disappears due to the plastic condition of the contractile elements. The time factor of this process depends on the physiological condition. In completely relaxed muscles it takes only a few seconds for the tension to disappear, in contracted muscle tension drops much more slowly.

Alexander We have done some work of that type which we have reported previously (32). We have abandoned that technique because of the problem of maintaining stabilized conditions in a stagnant bed. In other words, as we approach the final equilibration, we begin to get evidence of anoxic effects.

Shorr I had one question which I think I asked you before, but I do not know whether you had a chance to discuss it with the

Alexander I should say it was roughly comparable the weight of the leg is about 20 per cent greater I would guess however that the loop is more vascular

Let us now look at the actual pressure changes on the arterial and venous sides of the hind leg preparation which accompany the injection into the femoral artery Such a record is shown in Figure 51 Note that initially there is a steep rise in arterial pressure with no change whatsoever in venous pressure Arterial pressure reaches a summit and in this particular preparation the summit is followed by a drop in pressure even though the injection is continuing

Fremont Smith Is the injection made into the venous side or the arterial side?

Alexander The arterial side This was done because as I said one cannot inject the venous side of the hind leg

Burch What is the volume distribution?

Alexander At first it does not get to the venous side there is no immediate change in venous pressure

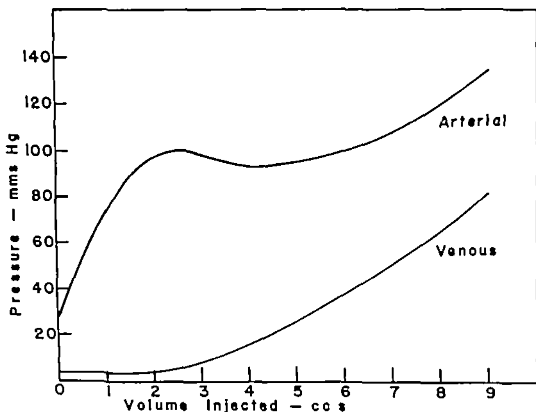


FIGURE 51 Arterial and venous pressures during the injection of blood at the rate of 60 cm³ per minute into the femoral artery of an isolated hind leg preparation.

pliance, resides for the most part in the smooth muscle In our own technique, and I think in many other techniques, this raises some serious problems in respect to what is frequently termed "vascular reactivity" This is illustrated in Figure 49 where, during the initial injections, the blood vessels were observed to be highly reactive After this initial distension, this vascular reactivity seems to have completely disappeared in the withdrawal curves

These phenomena must be taken into consideration in assessing many problems of circulatory homeostasis, blood volume distribution, and blood "pooling" Although any inferences in reference to the shock problem are still premature, I retain my suspicions that these mechanisms may have something to do with the blood volume that seems to disappear in shock

Heymans Dr Alexander, we gave you a hard time, but please consider it as an expression of a very marked interest, you are to be congratulated on your work

PRESSURE-VOLUME RELATIONS IN THE ISOLATED HIND LEG

Alexander Let us turn to consider the application of these techniques to the hind leg We prepared an isolated hind leg according to the same general procedure as that used for the intestinal loop, and repeated many of the same types of experiments, including the effects of different rates of injection and the actions of various drugs We observed many similarities with the type of response we obtained in the loop of intestine, and also some definite differences Rather than review all of these various experiments, however, I should like to confine myself to one particular problem which I feel may explain our failure to reproduce completely the intestinal results in the hind leg

If we refer back to the experimental setup illustrated in Figure 43, which we employed in studying the intestinal loop, we see that our technique must be modified because of the fact that the femoral venous system is valved It is therefore not possible to inject the femoral venous system directly, as we did in the case of the intestine The injector therefore had to be transferred to the arterial circuit supplying the isolated hind leg To evaluate what was going on in the vascular bed, however, we have recorded the pressure changes during the injection process on both the arterial and the venous sides of the leg circulation

Burch Does that provide an estimate of the volume of the vascular bed?

Alexander We have not developed a technique for that

Lawton Do you think it greater than that of the loop?

Alexander That appears to be impossible because of the valves in the femoral venous system

Fremont Smith If your venous pressure were a little higher to start with would it make any difference in this first part of the curve?

Alexander No

Fremont Smith Therefore you have clearly taken care of the problem of collapse

Alexander Yes I think so We started with 10 mm or higher of mercury and we obtained the same kind of curve

Lawton You have withdrawal curves that you will show?

Alexander Unfortunately we had trouble with withdrawal curves the valved venous system complicated our technique The ones we obtained were not valid

Fremont Smith Do you know anything about the state of the arterioles?

Alexander No except that the blood flow through these hind leg preparations is rather low I assume that they are in a state of spasm or possibly plugged with red cells I do not wish to argue with Dr Knisely on this latter possibility

Fremont Smith Is it conceivable that you have opened up the arterioles at the point where the venous pressure rises?

Alexander I definitely think it is conceivable as I will demon strate in a moment Before we examine the possibility however there is one further fact to be considered

Once the pressures in the vascular bed are raised to normal levels we find that the time required for transmission of pressure from the arterial to the venous side is approximately 0 15 seconds In other words if we suddenly stop and start the syringe with arterial pressures significantly over 100 mm. Hg, pressure changes are re flected to the venous side in this interval of 0 15 seconds This must be compared with intervals of the order of 2 0 seconds which are required for a rise in venous pressure to appear at the start of the injection as shown in Figure 51

To analyze this problem we made the assumption that blood does not flow from the arterial to the venous side of the vascular bed until a rise in venous pressure is observed, and we corrected our measurements to allow for the delay of 0 15 seconds which is the minimal time for the pressure volume increment to be trans mitted through the system

Nickerson Are these completely denervated, as in the case of the intestinal loops?

Burch That does not mean it is not arriving there, does it?

Alexander Possibly. However, the arterial pressure builds up very rapidly as the blood is injected, but the pressure rise does not appear on the venous side

Selkurt What was the rate of injection?

Alexander Sixty cm^3 per minute

Let us speculate a little more In the experiment shown in Figure 51, there is a fall in arterial pressure following the initial summit In some experiments there is merely a plateau instead of an actual fall, but in all cases the initial sharp upstroke of the arterial pressure is terminated It is approximately at this point, where the rapid rise in arterial pressure is halted, that we see the first evidence of a rise in venous pressure

What is happening in the vascular bed of the hind leg during this time? A volume of 2 cm^3 of blood has been injected during a period of 2 0 seconds For these first 2 seconds, however, we can find no evidence of this blood appearing on the venous side

Burch What is your evidence for that? The absence of pressure?

Alexander There is no pressure rise

Moe What is the state of the veins to start with?

Alexander I should say they are filled You will note that all these venous pressure values start from a finite level We have been very careful to keep a little positive pressure in the veins to avoid a collapse phenomenon In this case we had millimeters of mercury as our pressure Usually 5 mm , or higher, of mercury is selected, so we hope we avoid collapse

Comroe You do not have a pressure-volume curve on the venous side alone?

Alexander This is our attempt to get a pressure-volume curve We cannot anatomically dissect the venous side from the rest of the circulation

Comroe I mean in a large vein

Alexander We have not studied isolated veins

Burton Was the pressure in the artery only 30 mm Hg when you started injecting?

Alexander Yes As you recall, before we start our injections, we always cut off the arterial inflow into the preparation and allow time for the pressure to stabilize In the hind leg, we have found it necessary to allow 20 seconds for the arterial pressure to settle down to a stabile level

Selkurt Could you find out the answer to Dr Comroe's question by doing this experiment with an injection into the venous side?

Alexander That appears to be impossible because of the valves in the femoral venous system

Fremont Smith If your venous pressure were a little higher to start with would it make any difference in this first part of the curve?

Alexander No

Fremont Smith Therefore you have clearly taken care of the problem of collapse

Alexander Yes I think so We started with 10 mm or higher of mercury and we obtained the same kind of curve

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Fremont-Smith Is it conceivable that you have opened up the arterioles at the point where the venous pressure rises?

Alexander I definitely think it is conceivable as I will demonstrate in a moment Before we examine the possibility however there is one further fact to be considered

Once the pressures in the vascular bed are raised to normal levels we find that the *time required for transmission of pressure from* the arterial to the venous side is approximately 0 15 seconds In other words if we suddenly stop and start the syringe with arterial pressures significantly over 100 mm. Hg pressure changes are reflected to the venous side in this interval of 0 15 seconds This must be compared with intervals of the order of 2.0 seconds which are required for a rise in venous pressure to appear at the start of the injection as shown in Figure 51

To analyze this problem, we made the assumption that blood does not flow from the arterial to the venous side of the vascular bed until a rise in venous pressure is observed and we corrected our measurements to allow for the delay of 0 15 seconds which is the minimal time for the pressure volume increment to be transmitted through the system

Nickerson Are these completely denervated, as in the case of the intestinal loops?

Alexander Many of them have been denervated. The preparation shown in Figure 51 happens to have both the sciatic and femoral nerves still intact

Nickerson Does that make any difference?

Alexander Innervation exaggerates this effect

To understand what is happening to blood flow at the initiation of these injections, we have repeated brief injections in rapid succession into the femoral artery, as shown in Figure 52 The stopcocks in the arterial and venous circuits of the preparation were kept closed throughout, and the injections purposely given one immediately after another, so that the dynamic conditions would be altered for each successive injection

The vertical lines indicate the points 0 15 seconds in advance of the rise in venous pressure in each instance, which, as stated above, we assume to be the moment that blood started flowing through the vascular bed from the arterial to the venous side Corresponding arterial and venous pressures at these points are indicated, and below the tracing are shown the A-V pressure gradients

Following the well-known study of Whittaker and Winton (33), it is often assumed that a pressure of approximately 20 mm Hg is required between the arterial and the venous side before blood will flow If we examine the A-V pressure gradients observed in this experiment, the variation from 51 to 12 mm Hg reveals no suggestion of such a constant value It is similarly obvious that the venous pressures at the point of assumed initiation of blood flow show no uniformity Contrast these varying figures with those for the arterial pressure at the point that blood flow is assumed to start The initial value is at 62 mm , but the succeeding four values are all quite uniformly at the 41 to 42 mm Hg level

The experiment illustrated in Figure 52 is typical of others that we have done, in that the A-V pressure gradients at the point where arteriovenous flow is assumed to start have varied widely, yet the arterial pressures, following an initially high value, have been quite uniform Sometimes this arterial pressure level has been quite high In one experiment, for example, A-V pressure gradients varied from 111 to 42 mm Hg, while the arterial pressures showed an initial value of 119 mm , followed by four successive values which were all within the range of from 90 to 93 mm Hg

Burch What delay is there between each stepwise injection?

Alexander It is a matter of about 1 second However, we did not think that was critical for the particular point we are trying to establish here

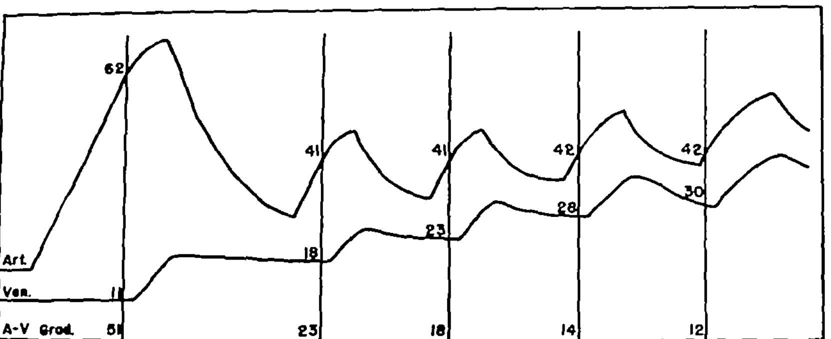


FIGURE 52. Arterial and venous pressures accompanying successive injections of blood into the femoral artery as described in text. This figure is semi-diagrammatic- considerable distortion of the time axis (abscissa) was necessary in order to condense the length of the original recording without obscuring the pattern of pressure rise.

Burton You then withdraw the blood?

Alexander No, because we wish to build up the venous pressure

Burch Could you give us the time interval from beginning to end?

Alexander The total time is 7-8 seconds

Burch What about the blood flow within the system?

Alexander During the intervals between injections, there is no rise in venous pressure in spite of a positive A-V pressure gradient I assume there is no blood flow to the venous side

Dawes However, you have no direct evidence that blood is not flowing?

Alexander That is right

Fremont-Smith You are saying that the flow, if any, is such that it could not raise the venous pressure?

Comroe I still think that unless one knows the pressure-volume curve of the *vein,* one does not know the magnitude of the volume change

Fremont-Smith Dr Alexander was saying that it is not enough to raise the venous pressure

Comroe However, it may still be large enough to cause considerable flow

Fremont-Smith The point is that Dr Alexander has no measurement of flow, but only of venous pressure All he is saying is that whatever flow there is, it is not enough to increase venous pressure

Alexander I think we are saying a little more In Figures 51 and 52, the initial portion of the injections produces a steep rise in arterial pressure without any change in venous pressure When venous pressure starts to rise, the rise in arterial pressure is interrupted Blood starts disappearing from the arterial side

Burch Not necessarily

Alexander Not necessarily, but probably

Fremont-Smith All you can say with certainty is that there is not enough flow to register on your pressure recorder

Alexander Yes, and at one point there seems to be a marked change in blood distribution

Burch The volume of blood necessary to produce that first venous change would be considerable

Alexander On the other hand, I am wondering whether we are not obtaining a first approximation to the distensibility curves for the two sides of the circulation In Figure 51, for example, I should like to think that the initial rise in arterial pressure, prior to any rise in venous pressure, is measuring arterial distensibility, the earlier portion of the rise in venous pressure, accompanied by

minimal changes in arterial pressure could represent venous distensibility I realize that I am begging the question in making such an interpretation

Comroe However with plethysmography in venous occlusion when one can actually see the veins is such a long latent period required for the veins to appear to be filling up?

Alexander In that case the pressure relationships are different Remember that in our preparation there is arteriovenous equilibration within 0 15 seconds if arterial pressure is normal To obtain the effect we have been describing arterial inflow must be occluded to drop the pressure down to a very low initial level

Fremont Smith It would be quite nice to be able to put a microscope over some venules and actually make a statement It would not take very much preparation Then we should be able to say when the column began to move how much that antedated the vascular pressure

Alexander I should like to hear a comment from the member of this group who has made just that type of observation (34)

Fremont Smith Dr Burton has not seen your preparation

Alexander However what he has done is almost the same thing Dr Burton I described my experiment for the specific purpose of introducing a discussion of your ideas on critical closure

Burton This is new ammunition I could use it to support my theories

Alexander A few months ago I told Dr Burton that I was anxious to discover some technique for proving that he was wrong I found the technique but it seems to prove that he is right

Burch In studies of digital blood flow by venous occlusion plethysmography a method which measures simultaneously and continuously the inflow and outflow of the human fingertip during a single pulse cycle shows that an increase in inflow on the arterial side at onset of the systolic phase of the pulse cycle precedes the increase in outflow by about 0 04 of a second

Alexander Essentially the same thing is observed in these hind leg preparations once the arterial pressure is elevated above a certain level In Figure 52 for example irrespective of the A V pressure gradient flow seems to occur readily from the arterial to the venous side once the absolute arterial pressure level of from 41 to 42 mm Hg is exceeded excluding the initial injection where the arterial pressure level was higher

Selkurt Is there any significance in the fact that your initial pressure is high in both instances? Would it follow that this would

alter the condition of the vascular bed, so that subsequent readings would be affected by the initial high pressure, which was 62 in the first instance, and 119 in the second?

Alexander Again I think we are dealing with some delayed compliance phenomenon

Selkurt That is why I asked

Alexander I would rather have Dr Burton work the delayed compliance phenomenon into critical closing theories than attempt it myself

Burton We have evolved an entirely new method of measuring critical closing pressure in humans It is an amusing thing, I think, and has arisen from experiments we were doing on the effect of posture on the blood flow of the digits

We were recording with one leg level, and the other at various angles to the horizontal, so that the control values from the level leg would tell us which of the reflexes such as the carotid sinus reflex, were central, and which would presumably be local, to the posture of that leg (Central reflex effects would be seen in both legs)

Working in digital plethysmography, many years ago, I observed (35), as have Dr Burch (36), Dr J Doupe (37), and others, that the spontaneous vasoconstrictions that appear periodically in the fingers, occur simultaneously with vasoconstriction in the toes Others showed that the spleen contracted at the same moment, and that these constrictions represented mass discharges in the sympathetic nervous system They are accompanied, as I showed, by an increased heart rate for a few heart beats, and are also accompanied by a slight rise of blood pressure It is a very widespread mass discharge of the sympathetic nerves

These discharges are modified by whether a man is warm or cold If he is cold, the discharges come very frequently, if he is warm, perhaps there is no constriction for five minutes All investigators have observed that if we record from two fingers on two hands, or two toes, and the digits are both level, the resulting curves are like one curve They go absolutely together

To my astonishment, something else occurred the first time I worked with one leg level and the other leg up All of a sudden, when the leg was raised up to perhaps 30°, the records of toe or finger volume, instead of fluctuating together, became mirror images of each other The volume of the toe of the leg which was up, increased in pulsation and in volume at the moment when the level toe constricted We were lucky enough to have flow measurements when this happened, and we saw that there was not only an increase

in pulsation and in volume of the toe but in blood flow at the instant when the toe of the level leg was showing the incidence of one of these spontaneous vasoconstrictions

Nickerson What is the duration of these variations?

Burton It comes down in 5 seconds — Dr Burch can correct me — and it takes 15 to go up again

Here is the dilemma you see I do not believe that because I have put this leg up the discharge in the sympathetic is now not reaching the vessels that are elevated Yet at the same instant when the rest of the vessels in the body are constricting at this upper level these elevated toe vessels show an increased flow and an increased pulsation size

How can this problem be solved? I think the answer is this when we studied pressure flow relations in a vascular bed (from the hind limb and ear of the rabbit and the human arm and finger) we found that when the vasomotor tone of the vessels is high the level of the blood pressure matters very much indeed If there is high vasomotor tone when we get to the point where we think the arterioles close an extremely small rise in pressure such as 1 mm will make all the difference between no flow at all and a considerable flow

On the basis of this we can explain the extraordinary disassociation of these curves when one of the limbs is lifted. We say that with the raising of one limb because of a drop in the hydrostatic pressure the vessels there have come to be in a critical condition They are near their critical closure They are on a very steep part of the flowpressure curve We also know that one of these vasoconstrictions is accompanied by a slight rise of blood pressure We know that on this part of the curve a slight rise of blood pressure is evidently much more important in increasing flow through these critical vessels than is any increase in tone that those vessels are sharing during a general vasoconstriction It seems to me that is the explanation.

Thus we think we can now measure the critical closing pressure very easily in the human We just take two fingers one from each hand, raise one hand, and keep the other in the level position We watch the records until the curves disassociate That is the critical condition, and the level of the fingers above the heart gives us a calculation of the critical closing pressure

Dawes How is the selection of those vessels made?

Burton The critical vessels are definitely arterioles There is no direct evidence but it all points to that.

Dawes They would be perhaps the most sensitive ones you are testing, because they produce this phenomenon

Burton Yes, they are capable of considerable tension in their walls for their small size Also, the correlation between critical closing pressure, and the resistance to flow at high pressures when the vessels are open, is extremely good It is 0 86, or something like that One of these two factors depends upon the critical vessels only, i e , the ones that are closed The other depends on all the vessels that offer resistance, of which we know the arterioles offer the major part The fact that these two measures are so well correlated means that the critical vessels must be the ones that offer the greatest resistance, namely, the arterioles

This paradox during vasoconstriction has some application, I think, to blocking agents, because some people have found that when they are ambitious enough to use blocking agents for peripheral vascular disease, where the vessels may be in a critical condition because of their high tone, that instead of obtaining an increased flow in the gangrenous toes, there is decreased flow The lowering of the general blood pressure may overshadow the fact that the tone of those diseased vessels has been lowered a little Thus, by giving a blocking agent in peripheral vascular disease, you may do the opposite of what you intended

Alexander It might be worth-while to point out that critical closure mechanisms are closely related to the problems which we presented at the outset of this discussion In reference to Figure 44, I emphasized that constrictor drugs intensify the sigmoid nature of the distensibility curve, producing a steeper slope at low pressures The steepness of this slope, being a consequence of the Laplacian effect, is an indication of a greater tendency towards critical closure in constricted vessels

Burch When studying the spontaneous volume waves, I observed five types One was associated with each pulse beat, a second with respiration There was a third type, called alpha deflections, and a fourth type slower and larger than the alpha waves, which we called the beta waves These were all superimposed on larger and much slower swings in volume, which we called gamma waves These five types of waves occurred at all times They did not follow each other concordantly 100 per cent of the time for contralateral finger tips, they varied about 80 per cent of the time (36) They tend to disappear almost entirely following interruption of sympathetic innervation to the part They also tend to disappear with marked dilation, such as is associated with exposure of man to a hot room

Incidentally simultaneous measurement of blood pressure with the Hamilton type of manometer failed to show a relationship with arterial blood pressure changes These waves were studied in the digits and pinna and perhaps represent a lending and borrowing phenomenon with exchange of blood in the skin with that in visceral organs and muscles In other words a man s blood volume is essentially limited at any one time so that it must be shifted from area to area of the body to satisfy local changes in tissue requirements This appears to exist continuously even during sleep

I should like to ask the physiologists if they have any data concerning the spontaneous volume changes for some of the visceral structures I did not study the spleen kidneys or liver for example

Burton There was a paper by Julia Herrick and Hiram Essex Professor of Physiology University of Minnesota * who studied simultaneous fluctuations in the volume of the spleen and they agreed with this

Green In muscle or skin vascular beds one rarely sees any cyclic changes in flow If present they are very minor as compared with the mean flow except when the animal is in very bad condition

Burch Are you referring to total flow?

Green Since there is not much cyclic change in flow the fluctuations probably average out in different areas even within an extremity Otherwise I should think one ought to see marked cyclic changes in flow

Heymans Don t you think that the outflow of the sympathetic plays a role in this mechanism of regulation and adaptation? I quite agree with your statement that the shift of blood is not only related to an arterial but also to a venous mechanism Therefore I think there is not only a passive but also an active adaptation of the veins to an afferent flow

Burton My own conviction is that the next five or ten years should be devoted to the study of the venomotor system

Heymans The venomotor system is certainly important. We are always talking about the arteriomotor system Reflexes on the venomotor tone related to arterial pressure have to come into the picture to a greater extent

REGULATION OF SYSTEMIC ARTERIAL PRESSURE DURING MUSCULAR WORK

Shorr Dr Liljestrand it is the consensus of the group that this meeting would be incomplete if we did not hear from you Would you talk to us about anything you care to?

*Personal communication

Liljestrand Within the vast field, "Mechanical Factors in the Regulation of the Circulation," it seems desirable to select some limited problems for discussion. Consequently, I shall deal with two important questions with which my own work has been concerned.

The first of these is the problem of the regulation of the systemic arterial blood pressure during muscular work. Von Euler and I (38), in 1946, recorded the pressure, during muscular work, induced by electrical stimulation of the hind legs by means of alternating impulses of increasing and decreasing strength, before and after abolition of the sinus and aortic mechanisms.

Figure 53 demonstrates the results obtained in the dog. In the normal animal there is an initial drop in the pressure shortly after the start of the work, but soon it begins to rise again and after some minutes attains about the same level as during rest. After section of the spinal cord between L_1 and L_2, that is, above the area of stimulation, muscular work has the same effect as before. This shows that the hypothesis put forth by Asmussen, Nielsen, and Wieth-Pedersen (39), that the regulation of circulation during muscular work is brought about reflexly by sensory impulses from the working muscles, cannot be correct. After denervation of both sinuses and section of the vagi, muscular work in the dog induced a much greater primary fall of the pressure, it was followed by a slow rise but did not reach the original level as long as the work was going on. When it had stopped, however, the pressure rose considerably above the resting value. Similar results were obtained in the cat and the rabbit.

From the experiments, it must be concluded that the sinus and depressor nerves convey impulses of paramount importance for the regulation of the arterial pressure during muscular work. It seemed of interest, however, to study whether both pressor and chemoreceptors are engaged.

We therefore tried the effects of carbon dioxide accumulation, as well as of oxygen want, the trachea of the animal being connected with a spirometer filled with oxygen or with air. In the former case, carbon dioxide was allowed to accumulate, in the latter, it was absorbed so that a continuous decrease of oxygen tension developed. As shown in Figure 54, carbon dioxide at first lowered the pressure and then induced a continuous rise. As is well known, it causes a dilation of the peripheral vessels, but this is at first largely counteracted by the presso-receptors. Later on, a strong stimulation of the vasomotor center is induced by the carbon dioxide, partly reflexly from the chemoreceptors, and partly directly

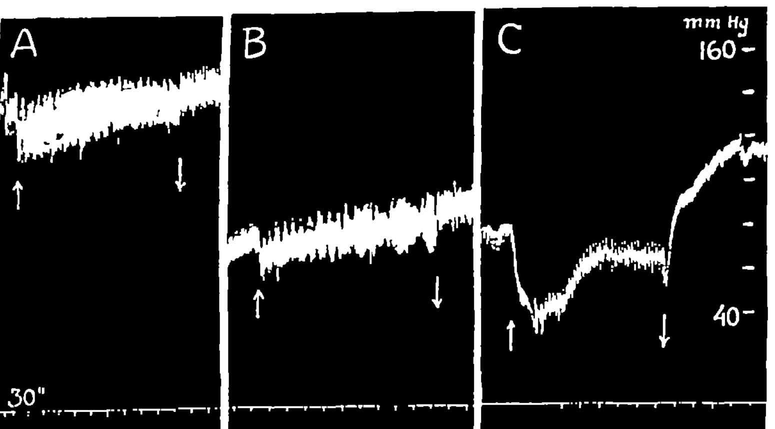


Figure 53. Dog, chloralose blood pressure recorded from femoral artery Between arrows muscular work. Between A and B section of spinal cord at the level of $L_3 - L_4$ Between B and C denervation of both sinus regions and vagotomy in the neck Reprinted, by permission, from von Euler U S., and Liljestrand, G The regulation of the blood pressure with special reference to muscular work. *Acta physiol scandinav* 12, 279 (1946)

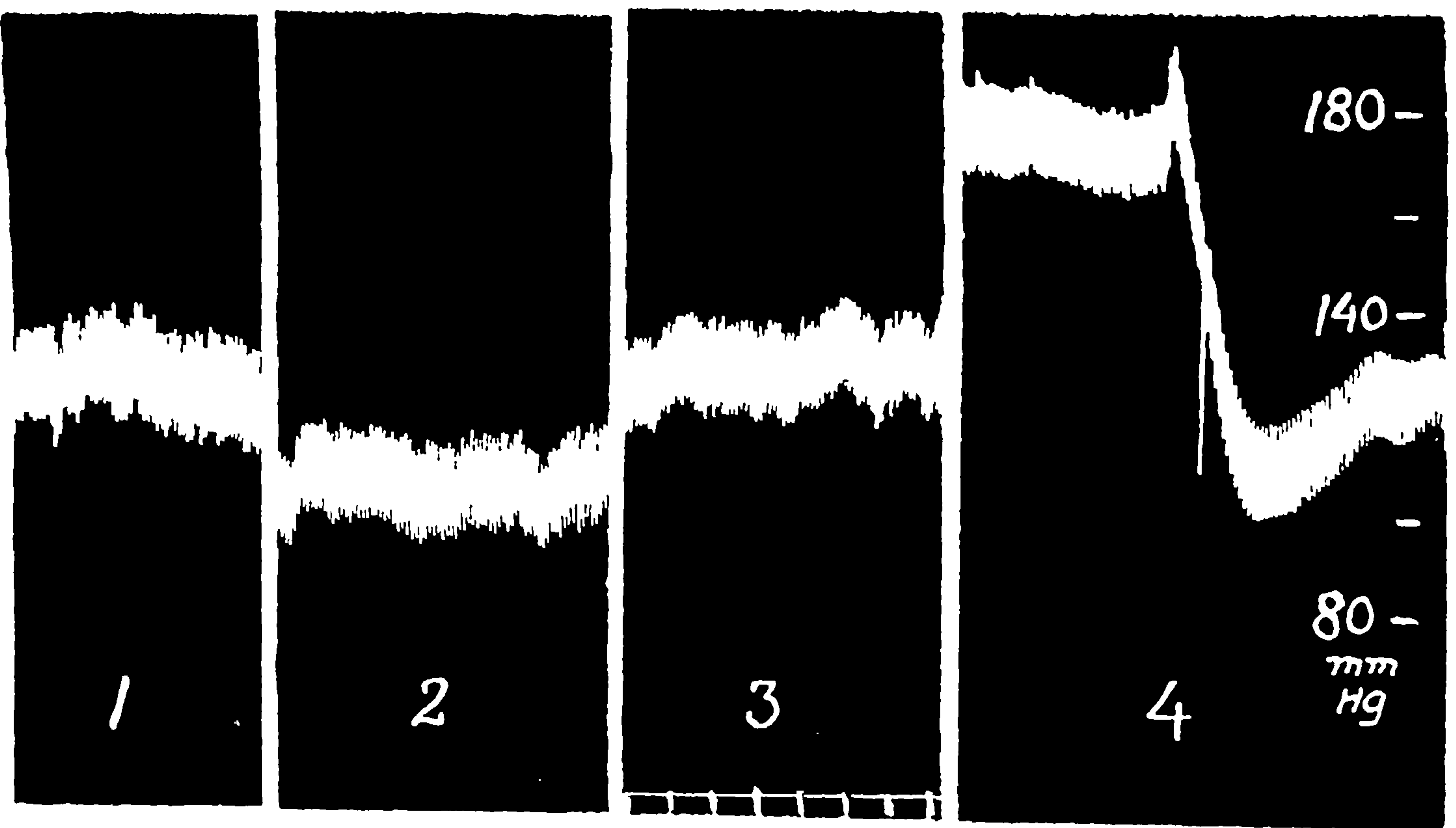


FIGURE 54. Cat, chloralose, blood pressure recorded from femoral artery. Animal breathing oxygen in a closed system with accumulation of carbon dioxide. *1*) (10.47) 5 p.c. alveolar CO_2, 2) (11.00) 8 p.c. alveolar CO_2, 3) (11.54) 20 p.c. alveolar CO_2, *4*) (12.50) 38 p.c. alveolar CO_2. Shift to air breathing. Time 30 seconds. Reprinted, by permission, from von Euler, U. S., and Liljestrand, G. The regulation of the blood pressure with special reference to muscular work. *Acta physiol. scandinav.* **12**, 279 *(1946)*.

The result is that the pressure rises That the presso-receptors are in a state of great activity is illustrated by the fact that the pressure fell below the starting value if air instead of the gas mixture rich in carbon dioxide were given suddenly The interpretation given is supported by the fact that after denervation of the sinus and aortic regions carbon dioxide induced a much stronger primary lowering and a greater secondary increase of the pressure than before After a small dose of ergotamine which eliminates the barocepter reflexes as well as blocks the vasomotor center to the action of carbon dioxide the primary lowering of the pressure after carbon dioxide was much greater than after complete denervation of the baroreceptor and chemoreceptor regions and persisted even after high concentrations of the gas the explanation being that carbon dioxide now produced only dilation of peripheral vessels

Oxygen want causes a rise in the blood pressure which is usually well compensated by the baroceptors If these are annulled with ergotamine it then induces a much greater rise As is well known the direct effect of oxygen want on the vasomotor center is mainly a depression

From the results obtained it seems clear that a rise in carbon dioxide pressure will be able to influence the blood pressure by causing a peripheral vascular dilation as well as by stimulating the vasomotor center directly and reflexly via the chemoreceptors Further a lowering of the oxygen tension will also stimulate the chemoreceptors though it will have the opposite effect on the center itself It seems probable that these results will have some bearing on the regulation of the blood pressure during muscular exercise Thus when the blood flow through the working muscles is inadequate i.e during static work, when the circulation may even be cut off a considerable rise in the blood pressure is often observed immediately after the work (40) This might be explained as due to the release of blood rich in carbon dioxide and poor in oxygen The great rise after work in our denervated animals with a reduced blood flow owing to the low pressure may also be explained in this way

We have performed some direct experiments which lend support to the view expressed Thus in the denervated cat, the return of the blood pressure after work was considerably increased if 6 5 per cent carbon dioxide was added to the inspired oxygen whereas no such effect was observed in the intact animal (Figure 55) Oxygen alone had a similar effect, which is to be expected since oxygen want would depress the center When a small amount of

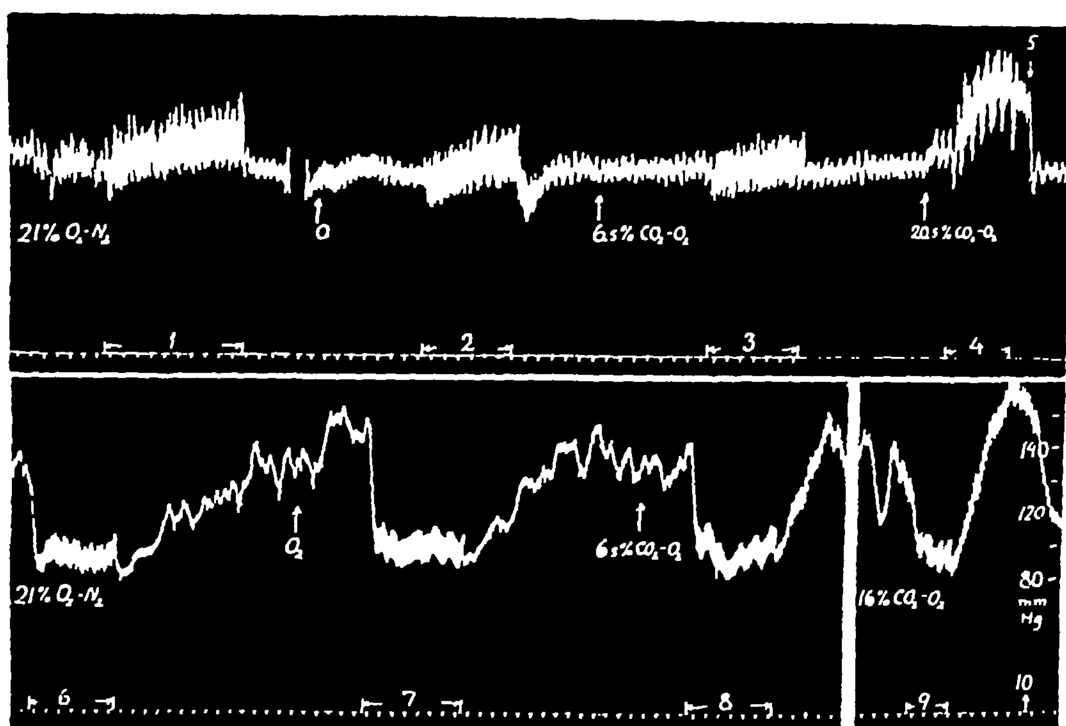


FIGURE 55 Cat, chloralose, blood pressure recorded from femoral artery. Between arrows muscular work *1-4* during breathing of *1*) air, *2*) oxygen, *3*) 6.5 p.c. CO_2 in O_2, and *4*) 20.5 p.c. CO_2 in O_2, *5*) shift to air. Between *5*) and *6*) denervation of both sinus regions and vagotomy. Muscular work during breathing of *6*) air, *7*) O_2, *8*) 6.5 p.c. CO_2 in O_2, *9*) 16 p.c. CO_2 in O_2, *10*) shift to air. Time 30 seconds. Reprinted, by permission, from von Euler, U. S., and Liljestrand, G. The regulation of the blood pressure with special reference to muscular work. *Acta physiol. scandinav.* **12**, *279 (1946)*.

ergotamine was given to the denervated cat, the pressure dropped much more during muscular work than before administration of, and the return to the normal level took a much longer time. This is in harmony with the assumption that carbon dioxide acts locally by causing a vasodilation, and that a counter-regulation, though abolished by ergotamine, normally sets in through stimulation of the chemoreceptors and the center. In our experiments, relatively low tensions of carbon dioxide caused a decrease, whereas higher concentrations led to a rise of the blood pressure. It is therefore to be expected that the central influence will become relatively greater as the amount of work increases. This seems to conform with the well-known fact that during light work the blood pressure is often maintained at a low level — sometimes even lower than during rest — but that it is raised during heavy work somewhat in proportion to the amount of work done per minute. Oxygen want in the intact animal acts essentially in the same direction as accumulation of carbon dioxide, the depressing effect on the center being under

ordinary conditions overcompensated by the reflex action through the chemoreceptors

Against the assumption of presso-sensitive reflexes as a link in the regulation of the arterial blood pressure Asmussen Nielsen and Wieth Pedersen (39) have objected that it is not easy to understand how the reflex reactions can be brought about at the onset of work because normally no initial fall in the arterial blood pressure is observed, and that it is hard to see how the change in vasomotor tone in the later stages of work can be maintained where the pressure shows no tendency to diminish but on the contrary is increased

With regard to the first of these objections it must be emphasized that a decrease of the stimulation of the presso receptors is not the only factor to be considered It may well be that other influences act simultaneously and prevent the primary fall in blood pressure in the intact animal although we have proved it in the anesthetized animal. As early as 1893 Johansson (41) concluded from his experiments that during work motor impulses to the muscles irradiate to the centers governing the heart This will explain why the first heart beat at the onset of work is already accelerated. It would seem possible that an irradiation might also influence the tone of the vasomotor center and counteract the initial lowering of the pressure especially if the onset of work is not quite sudden The second objection neither heeds the importance of the chemoreceptors nor considers the possible direct effect on the center Though the problem as a whole is complicated, I think that our experiments prove definitely that the presso-receptors and chemoreceptors during muscular work contribute greatly to the regulation of the blood pressure

INFLUENCES OF OXYGEN AND CARBON DIOXIDE TENSIONS ON PULMONARY CIRCULATION

The second problem to be discussed concerns the blood flow through the lungs The importance of the presso-receptors and chemoreceptors for the regulation of the systemic blood pressure, raises the question whether similar mechanisms exist in the lesser circulation Of course one must realize that the lungs being placed in series with the general circulation would scarcely be dependent on the maintenance of a certain pressure level in order to ensure the blood supply to the organ itself There would seem however to be reason for some regulation in order to avoid a harmful rise when the general blood flow was greatly increased Obviously

special arrangements may possibly be connected with the function of the lung

Von Euler and I (42) were unable, however, to demonstrate an influence on the pulmonary arterial pressure through nervous mechanisms under physiological conditions Clamping the carotids had only a very small effect on that pressure Indirect evidence of the relative independence of the pulmonary vessels from the sinus mechanism is afforded by some recent observations by Beznák and myself (43) Whereas clamping the carotids in the cat induced a considerable decrease in the flow of lymph from the left thoracic duct, presumably mainly due to lowering of the capillary pressure in the abdominal organs, the flow from the right thoracic duct remained practically uninfluenced

If the artery to the left lung were occluded, a very moderate rise followed in accordance with earlier experiences from different investigators This demonstrates the considerable adaptability of the pulmonary circulation to varying demands The explanation lies in the distensibility of the pulmonary vessels, and perhaps, as emphasized by Wagner (44), the opening of "reserve capillaries" Vagotomy, or the administration of ergotamine, had no influence on the result If the general flow of blood was increased from about 200 to 300 per cent by electrically-induced muscular work, the pulmonary arterial pressure rose in a similar way, as after clamping the left pulmonary artery, and this result was unaffected by vagotomy

If, however, the animal breathed different gas mixtures, pronounced effects on the pulmonary arterial pressure were obtained Moderate percentages of carbon dioxide increased the pressure, and the same was found during oxygen want Of special interest was the observation that oxygen and air produced different pressure levels (Figure 56) The increase produced by muscular work was superimposed on these levels Sometimes the transition from oxygen to air breathing was followed by a very considerable rise in the pressure, as illustrated by Figure 57 from Logaras' paper (45) This rise was not due to back pressure from the left atrium, the corresponding pressure curve showing only a slight fall It is out of the question that the great difference in pulmonary arterial pressure during oxygen and air breathing should be caused mainly by variations in the minute volume of the heart Therefore, it must be concluded that the vascular resistance changes Since vagotomy, extirpation of the stellate ganglions, and injections of ergotamine or atropine, had no influence on the effect of oxygen, this must be of local origin

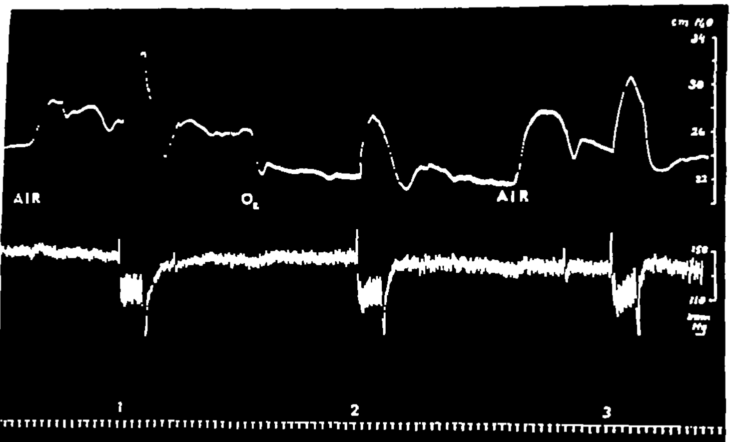


FIGURE 58. Cat, chloralose, blood pressure recorded from pulmonary artery (upper curve) and femoral artery At *1*) 2) and 3) muscular work. Time 30 seconds. Reprinted, by permission, from von Euler U S., and Liljestrand C Observations on the pulmonary arterial blood pressure in the cat *Acta physiol scandinav* 12, 301 *(1946)*

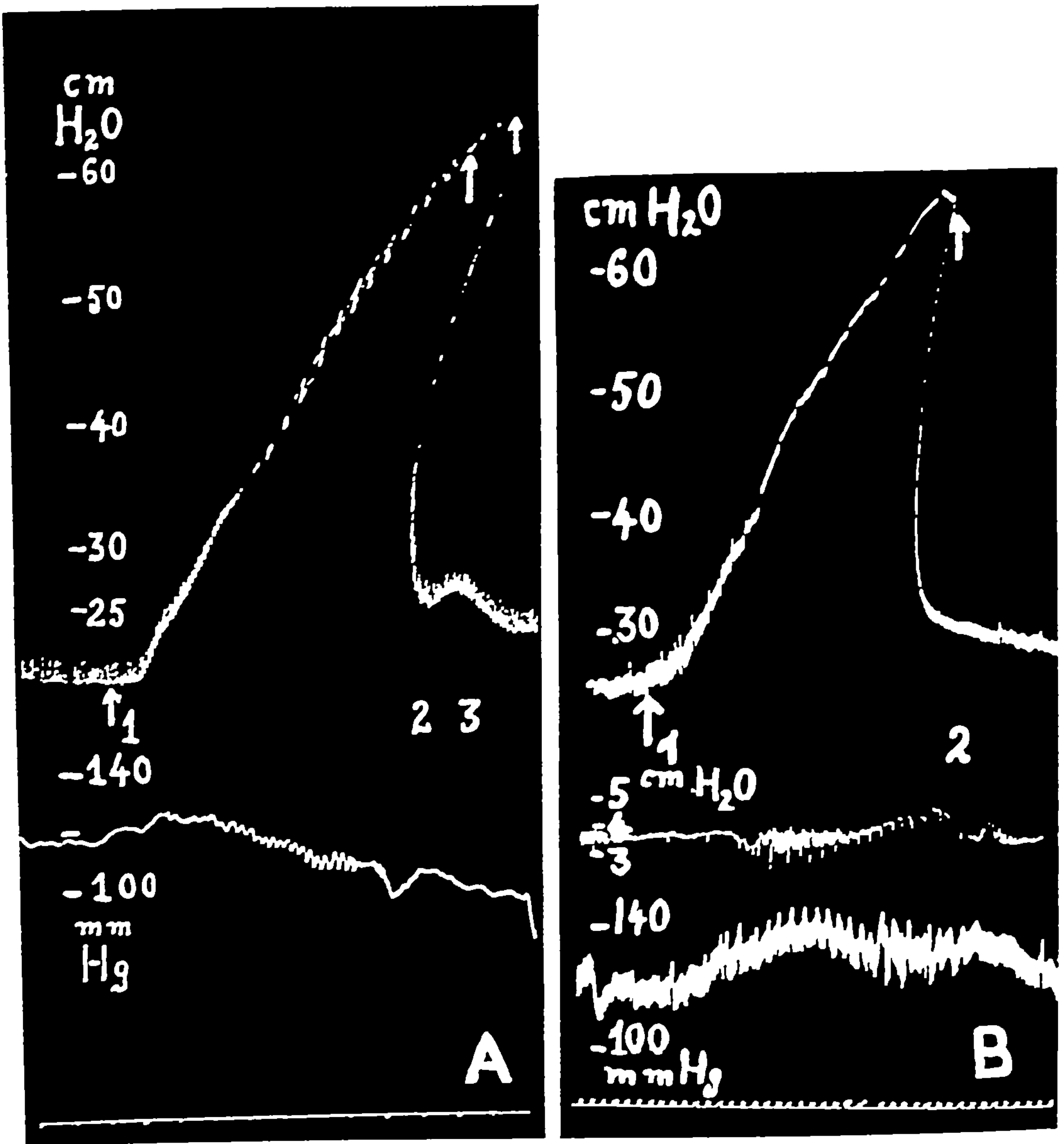


FIGURE 57A Cat, chloralose Upper curve pulmonary arterial pressure, lower curve systemic arterial blood pressure *1*) 15 p c O_2 in N_2 (from air), *2*) air, *3*) O_2 Artificial respiration. Time 30 seconds Reprinted, by permission, from Logaras, G Further studies of the pulmonary arterial blood pressure *Acta physiol scandinav* 14, *120 (1947)*

FIGURE 57B Cat, chloralose Upper curve pulmonary blood pressure, middle curve left atrial pressure, lower curve systemic arterial blood pressure Initially breathing 100 per cent O_2, then *1*) air, *2*) 100 per cent O_2 Spontaneous breathing Time 10 seconds Reprinted, by permission, from Logaras, G Further studies of the pulmonary arterial blood pressure *Acta physiol scandinav* 14, *120 (1947)*

Richardson What concentration of oxygen was used?

Liljestrand It was air and 100 per cent oxygen

The increased pulmonary arterial pressure during short term hypoxia has been confirmed in dogs by Aviado Cerletti Alanis Bulle and Schmidt (46) by Lewis and Gorlin (47) and by Stroud and Rahn (48) *Aviado et al* using 5 per cent oxygen in the inspired air observed an increased pulmonary arterial pressure Lewis and Gorlin however during moderate hypoxia corresponding to 10 per cent oxygen in the inspired air found a statistically significant increase in pulmonary vascular resistance but cardiac output did not vary significantly from control values During severe hypoxia cardiac output increased more or less and in this case the pulmonary vascular resistance remained unchanged or decreased (49)

Comroe Dr Liljestrand I am not quite sure about that tracing in Figure 57 B Is that pulmonary arterial pressure in a cat given oxygen then air and then oxygen to breathe and was the pulmonary arterial pressure 60 or 65 cm of water when the cat was breathing room air?

Liljestrand Yes

Comroe Is that not an abnormally high pulmonary arterial pressure?

Liljestrand It is very high Of course we obtain very high pulmonary arterial pressures after the operation we have done especially when the animal was breathing spontaneously

Comroe I see

Liljestrand It is a very big operation We have to open the chest put side-standing cannulae into the pulmonary artery and close the chest again Motley Cournand Werko Himmelstein and Dresdale (50) recorded increased pulmonary arterial pressure in normal man — on an average 90 per cent — when the subjects were breathing 10 per cent oxygen There was a small reduction of the cardiac output or according to a later publication (51) an increase in proportion to the severity of arterial anoxia. It was never large enough however to explain the pulmonary hypertension which accompanied it. Westcott Fowler Scott, Hauenstein and McGuire (52) found an average rise of pulmonary arterial pressure of 24 6 per cent in healthy subjects during inhalation of 13 per cent oxygen Doyle Wilson and Warren (53) during breathing of 10 per cent oxygen, observed a corresponding rise of 50 per cent the capillary pulmonary pressure remaining constant The increased pulmonary vascular resistance could not be explained by the moderate increase in the cardiac output.

Nisell (54,55,56,57), Hebb and Minno-Smith (58), Duke (59, 60,61), and Duke and Killick (62), have demonstrated, in the isolated perfused lung, the vasoconstriction caused by oxygen deficiency or carbon dioxide Nisell (56,57) has shown that if the isolated cat lung were perfused with blood that had been made hypoxic, or hypercapnic, in an oxygenerator, the pulmonary vascular resistance was reduced Inhalation of gas deficient in oxygen or containing carbon dioxide, on the other hand, gave the reverse response It therefore seems probably that either anoxia or carbon dioxide accumulation dilates the pulmonary arteries and arterioles, but constricts the pulmonary venules or veins

Our results have thus confirmed the generally accepted view that the pulmonary arterial blood pressure is not held at a relatively constant level to the same extent as the systemic pressure On the other hand, a special mechanism has been found in the lungs, by aid of which the degree of contraction of the venules, and thereby the local blood flow, can be regulated

It is tempting to interpret this finding as a means for correlating breathing and circulation If in some part of the lung the blood flow is insufficient in relation to the ventilation, then the alveolar air from that portion will contain more oxygen, and less carbon dioxide, than the rest of the lung Consequently, the venules in the first-mentioned part will dilate, and more blood will pass through, until equilibrium is again established As a matter of fact, Rahn and Bahnson (63), Atwell, Hickam, Pryor, and Page (64), as well as Peters and Roos (65) observed, in one lung of dogs during hypoxia, a reduction of the fraction of the total blood flow passing through that lung It is interesting that oxygen want, which is known to lead to vasodilation in the systemic circulation, acts in the opposite way in the pulmonary circulation In the former case, the "call for oxygen" of the different organs will become satisfied, and in the latter case, the flow of blood will be directed from parts of the lungs which are badly ventilated, to parts where the purpose of the lesser circulation can be better fulfilled Nisell's observation (55), that local alveolar oxygen excess through constriction of the bronchi decreases the ventilation of that part, whereas oxygen deficiency causes the opposite effect, indicates another mechanism that co-operates with the one just mentioned

The effect of hypoxia and hypercapnia on the pulmonary vessels are of interest from several points of view Thus, Cournand, and his group, showed that the mean pressure in the pulmonary artery in two of three normal subjects decreased during exercise, whereas

it increased in all eight of their cases with chronic pulmonary disease In three of these patients it was significantly elevated even during rest (66) According to Cournand (51) a linear correlation exists between the degree of unsaturation of the arterial blood and the degree of pulmonary hypertension Westcott Fowler Scott Hauenstein and McGuire (52) observed a definite decline in pulmonary hypertension during oxygen inhalation Thus anoxic elevation may be a contributing and reversible factor in pulmonary hypertension

The results obtained also seem to be of interest with regard to some other questions such as the decrease of the vital capacity observed during oxygen inhalation as well as some of the toxic effects of oxygen inhalation I will not enter into details at this occasion however

Nickerson Are these changes completely independent of innervation?

Liljestrand Yes We have found that neither vagotomy nor extirpation of the stellate ganglion has any effect Since it is found also in the isolated perfused lung it seems to be independent of innervation

Comroe Why do you believe that inhalation of high oxygen leads to a decrease in vital capacity?

Liljestrand By increase in the blood volume in the lungs

Comroe By constriction of the venules and dilation of the arterioles when there is an accumulation of blood in the capillary bed?

Liljestrand High oxygen will dilate the venules in which there is an accumulation of blood

Alexander Sarnoff and Berglund (67) have recently shown a markedly delayed compliance effect in the pulmonary vascular bed, which would I think, help to explain some of these pulmonary congestive mechanisms

Heymans Dr Liljestrand raised two interesting physiological problems The first one concerns blood pressure homeostasis and increase of arterial pressure during muscular exercise

I quite agree with him that the presso-receptors and chemoreceptors play an important role in the regulation of circulation during muscular work. But some other more peripheral mechanism may also be involved. Experiments on totally sympathectomized dogs showed indeed that when these animals are deprived of their efferent vasomotor pathways of reflex blood pressure regulation by means of the presso-receptors and chemoreceptors they not only

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regain a normal arterial pressure, but also are able to regulate their circulation during muscular work Totally sympathectomized dogs run and stay on the treadmill as well as normal dogs It is quite possible that, under normal conditions, blood pressure homeostasis, and regulation of circulation during muscular work occur mainly by means of the aortic and carotid sinus presso-receptors and chemoreceptors, but that in animals deprived of these receptors, some more peripheral mechanism takes over their function

The second interesting problem presented by Dr Liljestrand concerns the regulation of pulmonary arterial pressure and circulation Recent observations in our laboratory also showed, that while the systemic arterial pressure increases very markedly if the intracarotid sinus pressure has been decreased by clamping the common carotid arteries, the pulmonary arterial pressure, on the contrary, does not increase, or if so, only slightly Systemic and pulmonary arterial pressures thus react in a different manner to the carotid sinus reflexes

Another recent observation showed that a large amount of bleeding provokes a marked drop of systemic arterial pressure, but no alteration in pulmonary arterial pressure May I ask Dr Liljestrand if this phenomenon could not be related to his findings showing that oxygen want raises the pulmonary arterial resistance?

SYMPATHETIC VASOMOTOR FIBERS

Liljestrand The regulation of blood pressure during muscular work after sympathectomy is a fascinating problem which must be investigated closely I remember two old experiments by Goltz (68,69) on different vasomotor mechanisms If one were abolished, by section of the vasoconstrictor nerves, another took over the function after a week or a month Obviously, something of the same kind is happening here However, I think it is essential that it be investigated closely

Heymans The organism employs a number of different mechanisms to regulate the circulation Ruling out one mechanism, which is fundamental in normal conditions, could activate the complementary adaptation of other mechanisms which normally are less important However, I agree that this possibility ought to be investigated further

Folkow In connection with what Professor Heymans has said, I should like to mention the recent series of experiments by Hertzman, *et al* (70), who found that in dogs, where the sympathetic chains had been completely removed, evidence was obtained of remaining constrictor fibers which during their whole

course run in the ventral roots to the peripheral nerves and thus are not eliminated by what we call a total sympathectomy. Perhaps these remaining "ventral root sympathetic fibers" take over in part the nervous control of the circulation because the vessels are then to some degree sensitized to the mediator substance. I do not know the exact fraction of constrictor fibers taking this special route nor whether all animals have them, but they seem to be able to elicit significant vascular effects.

Acheson: Did I understand you to say that the sympathectomized dog has no change in blood pressure upon stimulating the sensory ends of a cut sensory nerve?

Heymans: No. In totally sympathectomized and vagotomized dogs reflex or central stimulation does not induce any increased rise or fall of arterial pressure. Neither could we find any efferent vasomotor outflow from the central nervous system to the spleen, kidney or limb. The function of the constrictive fibers running in the ventral roots without going into the sympathetic ganglionic chain thus has still to be investigated.

Folkow: Professor Heymans, some years ago you wrote a paper concerning the effect of carotid occlusion in totally sympathectomized dogs; you were able to obtain a rather marked rise in blood pressure on carotid occlusion, were you not?

Heymans: Yes.

Folkow: I believe you concluded that there probably were some vasomotor fibers not running via the sympathetic trunks which were responsible for the pressor responses. Wouldn't the extra sympathetic vasoconstrictor fibers which Hertzman *et al.* (70) found running in the ventral roots be a probable pathway for this remaining carotid occlusion reflex?

Heymans: Experiments with Bacq and Brouha (71) showed that in totally sympathectomized cats vasomotor carotid sinus reflexes may occur during a certain length of time after sympathectomy. In cats vasomotor outflow thus may be present outside of the sympathetic, although the possibility of regeneration and reconnection of sympathetic fibers may not be excluded.

PRESSURE FLOW RELATIONS

Folkow: I should like to make some comments about the stress relaxation phenomenon which has been mentioned. In a vein with a given wall tension, if the intravascular pressure is suddenly increased, the tension is at first raised but will then vanish due to relaxation of the smooth muscles in the wall of the vein. This seems to be easily demonstrated as regards veins but this type of reaction

does not occur with the smooth muscles of the small arterial vessels, which are mainly responsible for the peripheral resistance, at least not when the pressures applied are within reasonable limits Suppose we measure continuously the perfusion pressure, and the blood flow, through the muscles of a cat's limb The vessels are denervated, thus excluding vascular reflexes, but also under such circumstances the blood vessels of the muscles have a high "inherent" tone, so that the vascular area is far from being maximally dilated To give reasonable figures the peripheral resistance under such circumstances is roughly from 5 to 6 times larger than it is when the smooth muscles are maximally relaxed by, e g , large amounts of vasodilator drugs If stress relaxation really occurred as regards the small arterial vessels, it would mean that a sudden increase of pressure would induce a huge increase of flow, not only because of the raised pressure, but also because of this particular stress relaxation, which would markedly decrease the peripheral resistance However, this is not what normally happens Immediately upon a pressure rise one generally can observe a certain drop in peripheral resistance, probably due to a purely physical distension of the vascular bed, induced by the sudden increase of intravascular pressure The peripheral resistance begins to increase again when the reaction, which takes from 30 to 60 seconds, is completed, and in most cases will be even *higher* than it was before the pressure rise In other words, when the reactivity of the vessels is good, they respond to a pressure rise with a constriction If the tone of the blood vessels is poor, and the reactivity of the smooth muscles is decreased or abolished, this type of reaction is not seen, but only the purely physical effects of the pressure changes, as distension and viscosity variations In analogy with this, a pressure drop induces first a certain elastic recoil, soon counteracted and mostly overpowered by a relaxation of the smooth muscles of the vessels, so that the net effect will be a drop in peripheral resistance If the vessels already are maximally dilated at the moment of pressure drop only the elastic recoil will occur and then the peripheral resistance will increase Thus, as long as the basal tone is good, the denervated vessels will respond to pressure changes in such a way as to keep the blood flow as unchanged as possible, a response pattern which, in the intact animal, is often masked by the influence of the vasomotor nerves, whose effects are stronger than these local responses Now, as this type of response means a constriction, induced when pressure is raised, it is in fact the opposite to the stress-relaxation phenomenon The background of these reactions

is probably a complicated affair involving several cooperating factors and further they are not equally well pronounced in all vascular areas I have perfused the whole vascular area in kittens by way of a donor cat The vessels of the kitten were denervated by way of destruction of the spinal medulla in order to eliminate vasomotor nerve reflexes This total vascular area of the kitten showed principally the same reactions as were described for the vessels of the muscles thus indicating that even if some vascular regions may behave practically as passive elastic tubes the reactivity of the vessels in other areas is so pronounced that the net effect will be dilation as a response to lowered perfusion pressure and constriction when pressure is raised Under such circumstances the factor *n* in the formula

$$\text{Flow} = c \quad \text{Pressure}$$

will be below 1 The less pronounced these active responses are the higher will the factor *n* be In cases where due to the experimental conditions or other circumstances there are practically no active smooth muscle reactions the factor *n* might be far above 1 as factors such as distension by pressure increase and viscosity changes with changed flow rates are now unopposed

I discussed these reactions with Dr Zweifach and asked him what can be observed under the microscope when pressure is increased in the small blood vessels If I did not misunderstand him he said that one generally can observe a certain increase of vascular diameter which after some latency is followed by a constriction Isn t that right, Dr Zweifach?

Zweifach Yes

Heymans Dr Folkow how did you change pressure in your experiments?

Folkow By partial occlusions of the supplying artery easily graded to any pressure level as the inflow pressure to the limb was continuously recorded below this partial occlusion

Heymans And in what ranges were you changing blood flow at the same time?

Folkow I measured the blood flow continuously the inflow pressure and the venous pressure I could change both these pressures within a very wide range and keep them at any given level for a long time It was then possible to study the effect on the blood flow and the peripheral resistance because they can easily be calculated at any moment from these three measurements

Heymans Are your observations related in some way to the

observations of Bayliss (72) on the peripheral vascular reaction induced by short-lasting interruption of blood supply?

Folkow Yes, and they are related to many other papers

Heymans Bayliss observed that short-lasting interruption of blood supply to the limb, provokes a marked peripheral vasodilation Thus changing pressure, and blood flow at the same time, could induce vascular responses which are not related to the pressure variations, but to the alterations in blood flow and oxygen supply I think the responses of peripheral vessels to decrease of arterial pressure are mainly due to the reduction of blood flow

Folkow I believe too, that the resulting change of flow is a most important factor, but there is evidence that it is probably not the only factor responsible for these types of vascular reactions However, it is obvious that if the pressure, and thus the flow, is lowered, the oxygen supply and the elimination of possible vasodilator metabolites will be interfered with, while the tissue metabolism will go on as before A relative oxygen lack, and a certain increase of metabolite concentration, will be the result, factors which induce a relaxation of the smooth muscles of the blood vessels

Heymans The peripheral vasodilation in the leg, provoked by a short lasting occlusion of the femoral artery, remains quite a time after the restoration of a normal blood supply Did you measure the peripheral resistance in the leg?

Folkow Yes, it can easily be calculated at any moment, as both pressure and flow are continuously recorded

Heymans Did you decrease the arterial pressure in the leg by the clamping of its artery?

Folkow Yes

Heymans But at the same time you have changed the blood flow and oxygen supply What happens to the peripheral resistance?

Folkow Immediately after lowering the arterial pressure, the peripheral resistance goes up, due, at least to some extent, to an elastic recoil of the vessels when the intravascular pressure is lowered

Heymans How can you measure the peripheral resistance at the moment the artery is clamped if there is no blood flow?

Folkow But in these experiments I have not occluded the arteries completely, it is only a partial obstruction, so that flow still goes on at a lowered pressure head

Heymans However, the blood flow has been decreased

Folkow Yes, the flow is decreased when the pressure is decreased,

but as I measure both these things I can always obtain the peripheral resistance and thus get some idea about what is happening to the vascular transverse sectional area when pressure is changed

Heymans Clamping the femoral artery for a few seconds we could not measure the peripheral resistance during this decrease of blood flow but immediately after unclamping the artery and restoring the afferent pressure As in the observations of Bayliss the peripheral resistance was observed to be decreased during a period after clamping and unclamping the femoral artery

Comroe Do you measure pressure and flow to obtain peripheral resistance?

Heymans We used the method described by Nolf (73) registering the peripheral pressure in the *arteria femoralis profunda* This method permits us to register the peripheral resistance related to the arterial pressure

Knisely It is a measurement of pressure then? In what units do you state it?

Heymans A mercury manometer was used but other methods for measuring pressure may also be employed I believe that reactive vasodilation is induced by a reduction of blood flow and oxygen supply Oxygen requirement is a local regulator of peripheral resistance and blood flow

Folkow That mechanism is certainly one of the most important but I do not think that it is the only factor in these vascular reactions If the artery is totally obstructed and there is no blood flow it is of course impossible to measure the peripheral resistance but in my experiments I have not worked with total obstructions but only partial ones which lower but do not eliminate the pressure head.

Alexander The renal physiologists for a number of years have been making much of an autonomous regulation of renal circulation I think many of them thought they had a unique problem Actually coronary blood flow exhibits much the same behavior tending to return to the original rate of flow after changes in arterial pressure (74) This autonomy seems to relate to the local oxygen requirement In some of our own observations on the intestine blood flow reacts to pressure changes in the same fashion as you report for the leg. This seems to be a relatively universal phenomenon However the question of whether we are dealing with chemoreceptor or pressoreceptor mechanisms is not clear

Selkurt Your findings are quite parallel to what happens in the kidney When the pressure is suddenly raised there is a momentary

transient rise in flow, and then in about a minute it comes down again. If the pressure is dropped, the reverse occurs.

It is interesting to hear you comment that it is a problem of the reactivity of smooth musculature. We have been thinking along the lines of the metabolic side, as Professor Heymans brought out. Certainly when pressure is decreased and flow impaired, it is conceivable that you would have dilator metabolites being produced. The only disturbing thing is that I do not see how the reverse phenomenon, raising pressure and increasing flow, would in any way encourage the production of vasoconstrictive phenomena, because the blood is thoroughly saturated with oxygen before and after this process. How can you account for the reverse trend?

Heymans In your experiments, Dr. Folkow, the leg was decentralized by cutting the nerves. The peripheral resistance thus was already decreased, and the blood flow increased as a result of the vasodilation occurring after section of the vasomotor nerves.

Folkow I worked chiefly with denervated vessels, but as regards the blood vessels within the muscles, they still have a pronounced tone after the vasomotor nerves are cut.

Heymans However, the vascular tone is at a low level related to normal.

Folkow The difference is that the blood flow through the muscles is approximately doubled when the normal constrictor discharge is eliminated by cutting the nerves.

Heymans That means quite a decrease in the peripheral resistance.

Folkow Yes, but these denervated blood vessels may be dilated much more by muscular work or injection of acetylcholine, in fact the flow can generally be increased from 5 to 7 times in a cat, which means that the basal "inherent" tone of these vessels is very pronounced.

Heymans May I point out that tissue oxygen want not only acts directly, but also affects the vasoconstrictor impulses reaching the blood vessel from the vasomotor innervation.

Selkurt This also happens in the denervated kidney. Therefore, it has to be something beyond any neuromuscular relationship. It would have to be some direct influence on the musculature.

Heymans I do not exclude the influences of pressure variations on the peripheral resistance, but I still wish to point out that changes in blood flow occurring simultaneously with blood pressure variations, may also induce modifications in the peripheral resistance. The question then arises: which part of the vascular

reactions is due to the pressure variations and which part is due to the changes in blood flow?

Selkurt Your point is well taken

Heymans I would agree on the point that variations of blood pressure blood flow oxygen requirements and metabolites may act on the peripheral blood vessels and thus on the peripheral resistance

Folkow These types of vascular reactions are rather complex probably involving many factors and when I say that a pressure change induces a given flow change I do not wish to give the impression that the pressure change as such is the only factor operating and causing these changes in vascular tone and thus in flow On the contrary I am quite sure that the resulting change of flow is the most important one as it will influence the oxygen supply and the elimination of vasodilator metabolites both of which factors have important effects on the tone of the vessels

May I answer the question Dr Selkurt raised some minutes ago? Suppose we increase the pressure above the normal level and thus increase the blood flow everything else in the condition being unchanged We know that the metabolism intimately regulates the local blood supply probably by way of production of vasodilator metabolites present in higher concentrations when metabolism is raised, thus dilating the vessels Now in this case we have a steady metabolism and thus a steady production of metabolites creating a continuous dilator influence on the vessels A raised pressure with the consequent increase of flow will allow a better elimination of these metabolites Their concentration in the tissue spaces surrounding the blood vessels will then be lowered which reduces their vasodilator influence on the vessels consequently increasing vascular tone to some degree It is in principal the same mechanism as when pressure is lowered just taken the other way around.

Nickerson I should like to put in one point which we obviously do not have time to discuss fully I think it is clear that the denervated smooth muscle of vessels can act to regulate flow in response to factors other than metabolites I am referring to animal work done in other laboratories and to some observations we have made on a boy with Morvan's syndrome and apparently no peripheral sympathetics whatever The basic observation is simply that as an extremity is cooled, the blood flow remains essentially unchanged until a critical temperature is reached at that time a rather sudden constriction of the vessels occurs The reverse is seen as the extremity is warmed. If this were a metabolic effect, a more gradual

response would be expected. There is not a sudden change in metabolism at, let us say, 22° C. ambient temperature. Thus, although metabolic effects certainly can be involved in the regulation of vessel caliber, I think we have to recognize that the smooth muscle, independent of its innervation, can respond to stimuli other than metabolites.

Green: I would agree with Dr. Folkow thoroughly that these observations are true in a muscular vascular bed, but when one repeats the experiment in an isolated cutaneous bed, one does not see this phenomenon. This again fits in with the idea that it is a metabolic phenomenon which is responsible, and not any pressure distensibility phenomenon.

Folkow: The vessels of the skin do not exhibit much of an "active" response to pressure and flow changes. They seem to remain rather uninfluenced by pressure changes, being only to some degree distended as pressure is increased. However, the cutaneous vascular area has an abundance of arteriovenous anastomoses, which probably are responsible for the main part of the blood flow in preparations where the vasomotor nerves are cut. They are rather large vessels, and there is some experimental evidence indicating that the most pronounced reactivity is found in the smallest arterioles and precapillary vessels. The vascular tree there is very different and specific, which might partly explain the different pressure-flow relationship. Do you agree to that?

Green: One still obtains the same curve, whether the tone is high or low.

Folkow: That is interesting.

Green: Practically no reactive hyperemia occurs in the skin.

Folkow: As regards the skin blood flow I have only worked with denervated preparations, and I obtained results which were similar to yours, with flow increasing proportionally more than the pressure. This was probably due to passive distension, and a certain decrease of effective viscosity as flow was increased.

Green: The same thing occurs in either the denervated or innervated leg.

Folkow: However, I think that only a rather small part of the different vascular areas in the body show a pressure-flow relationship like that of the skin vessels. If the total peripheral resistance is measured in animals where the blood vessels are denervated, it will be found that the resistance increases somewhat as a response to an increased pressure, while it decreases when pressure is lowered. This means a reaction of the same type as is seen in the muscles

However the reactivity and the tone of the vessels must then be good if the vessels are nearly maximally dilated they will behave more like passive slightly elastic tubes

Burton I think Dr Folkow s experiments are interesting indeed I should tend to agree with Dr Green We have not seen this in other vascular beds perhaps it is something rather peculiar to muscle It would be important for him to settle whether or not this reaction of the smooth muscle comes from the pressure change or from chemical factors Perhaps it is possible to do this since the venous and arterial pressures can be changed independently I would suggest experiments in which the mean pressure or the pressure of all vessels was increased but the blood supply kept constant This would provide a separation of the pressure and flow factors

Folkow I have done so in some experiments I decreased the blood flow to a given level for a short period either by lowering the inflow pressure and thus the intravascular pressure or by increasing the venous pressure by which the mean intravascular pressure was increased a little But in both cases the blood flow was reduced to the same extent However for the most part the resulting reactive hyperemia was considerably more pronounced in those cases where the arterial inflow pressure was reduced in other words the vascular smooth muscles relaxed more when intravascular pressure was lowered I could find no other explanation for these experimental findings — besides the obviously important factor caused by accumulated metabolites — than that a different but cooperating mechanism must exist Denervation and consequent degeneration of the nerves did not seem to influence the reactions which seemed to point to the smooth muscle proper as the factor reacting to the change in intravascular pressure One cannot definitely exclude some local nervous mechanism but so far as I know there is no histological or neurophysiological evidence at present that a local vasomotor nervous plexus will survive in the periphery when the efferent vasomotor nerves are degenerated Local ganglion cells are said not to exist around the peripheral blood vessels But naturally one does not feel too sure about these things

Selkurt In the kidney when renal venous pressure is elevated it is interesting to find this parallelism again In other words the flow goes down almost linearly with the A V pressure decrement if you decrease it with venous pressure elevation

Burton I find myself very resistant to the idea that an arteriole or artery can respond to an increase of pressure by getting smaller

This seems to me something which would lead to a very unstable situation. I also find it difficult to see how reactive hyperemia works on the arterial side, because the blood is flowing from the artery to the venous side. The metabolic factors would be acting further down, I should think. I am beginning to think that a reflex of some kind, if you can call it a reflex, from the venous side affecting the arteriolar side, is perhaps more concerned in this phenomenon than anything else.

Folkow: It is quite possible that it is so, but then we must reconsider our views about the principles of the nervous arrangements controlling the blood vessels, e.g., independent local nervous plexa uninfluenced by decentralization, and consequent degeneration of the efferent and afferent fibers. I do not know of any direct evidence for such an arrangement, most investigators seem to reject this possibility.

Burton: This reflex I mentioned, if you can call it a reflex, is completely independent of central connections.

ELASTICITY OF ISOLATED AORTIC STRIPS

Lawton: In our studies of the elasticity of the isolated strip from the aorta, it has become apparent that there is what you might call an "operating point" for the behavior of the aorta. If I may, I should like to show a few figures just for clarification. Everyone is willing to admit that the elasticity of the aorta is a very nonlinear affair. If one suspends a piece of the aorta from clamps, loads it and then displaces it slightly and lets it vibrate, one can determine (75) the natural frequency of free longitudinal vibration and also the decrement, and from this make some calculations as to its elasticity and viscosity at a given length or weight (Figure 58).

Fremont-Smith: In what direction is the strip taken?

Lawton: We have taken them both circumferentially and longitudinally. We have not found any particular difference.

Nickerson: What animal?

Lawton: This one happens to be the dog. In Figure 59 we have plotted the natural frequency on the vertical axis and the relative change in length, α, on the horizontal axis. The ordinate is $\frac{\omega_2 \underline{L_0}}{\underline{g}}$, $\underline{g}$ being the acceleration due to gravity, and $\underline{L_0}$, the resting length. We took all these factors together for theoretical purposes, but $\underline{L_0}$ and $\underline{g}$, of course, are constants in this experiment. The lower curve represents an aorta taken post-mortem from a young individual who had committed suicide. It was a fairly fresh specimen from a

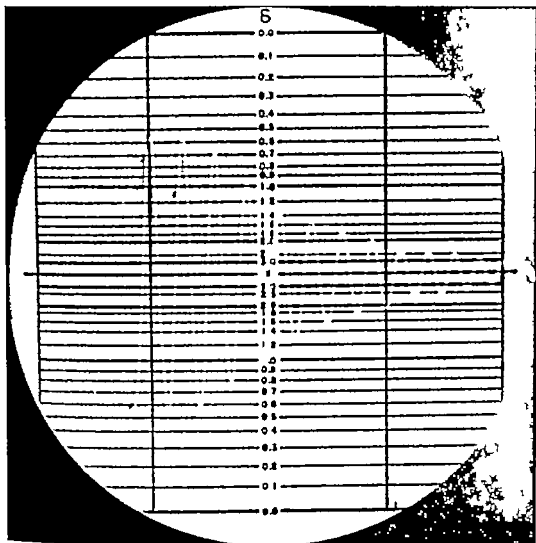


FIGURE 58. Free longitudinal vibration in an isolated longitudinal aortic strip of the dog. This oscilloscope tracing was made by photoelectric measurement of the amplitude of the vibrations at the lower end of the strip. The amplitude declines in a logarithmic fashion with time. When plotted on semilogarithmic coordinates, the slope of the straight line produced is the logarithmic decrement.

21 year old man. The upper one represents a 70-year-old man. The curves characteristically have minimum points. If one uses the pressure tension radius relationship one can ascertain what the intra arterial pressure ought to be at these minimum points.

Burton Could you tell me what alpha is?

Lawton Alpha is the relative length that is the stretched length divided by the unstretched length. It begins with one you see. For the young individual this represents a total stretch of from 80 to 90 per cent. All the specimens that we have examined have such mini

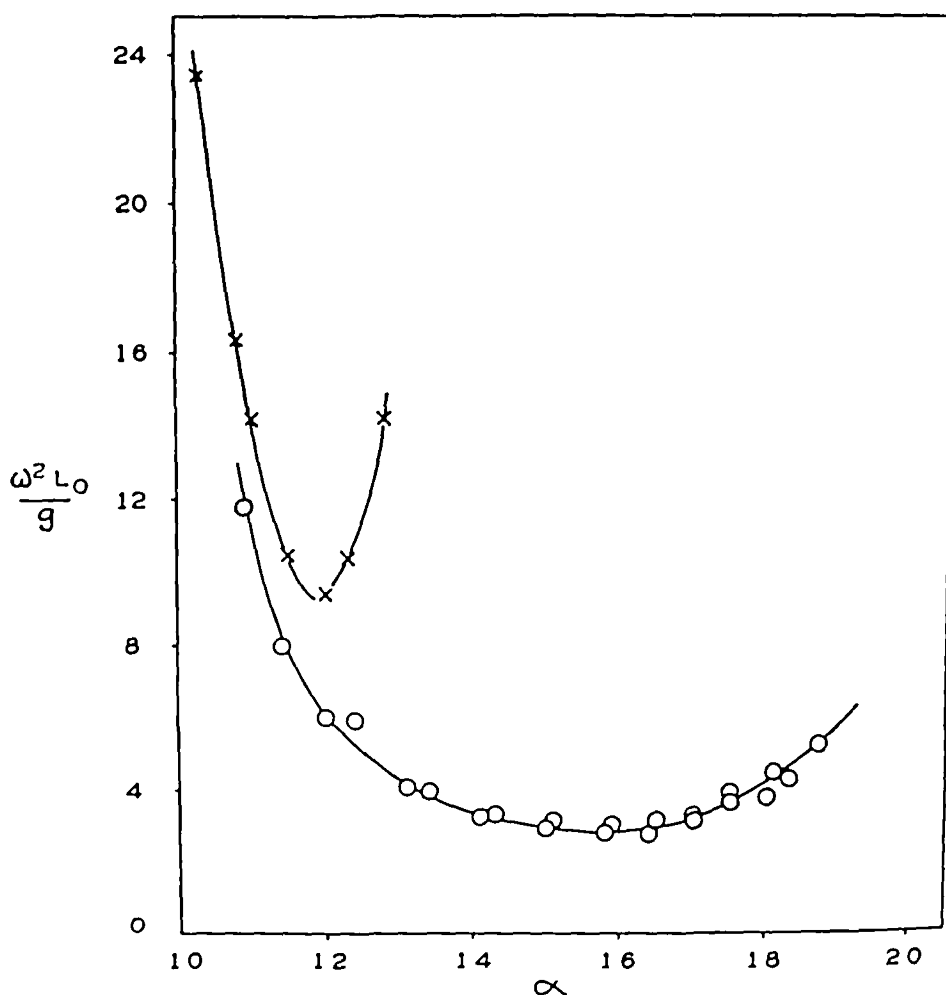


FIGURE 59 The influence of age on the frequency response of isolated aortic strips $w = 2\pi f$, f-frequency Open circles 21-year-old male, crosses 70-year-old male Reprinted, by permission, from Lawton, R W, and King, A L Free longitudinal vibrations of rubber and tissue strips *J Appl Physics* 11, *1340 (1951)*

mum points If one examines the aorta of a dog from the region of the arch all the way down to the abdominal region, one finds that these minima vary from 70 to 80 mm Hg up to around 120 or so In general, the more extensible specimens have the higher pressures at the minimum point In this older individual, the minimum point would probably be around 70 mm Hg

Burton You have not had aortas from persons with hypertensive mean pressures of 200 mm as yet?

Lawton No However, perhaps this matter of an "operating point" has some bearing on homeostasis of blood pressure If one examines the viscosity, one finds that it also goes through a minimum at approximately the same point as the natural frequency Thus, this

is a kind of energy valley affair and the blood pressure moves with reluctancy up either side of the valley

Alexander In view of what we know about muscle would you care to speculate on what would happen to this minimum point in a vessel as it became constricted?

Lawton Looking at your work I should say that the minimum point would shift toward a higher pressure in a contracted case

Knisely What do you mean in terms of physics by the viscosity?

Lawton What we have done is to compute the logarithmic decrement from that curve that you saw and then use that as our measure of the viscosity One can also obtain a coefficient of viscosity if one likes by taking into account the cross sectional areas and a number of factors

Knisely Do you mean inter molecular friction in the solid?

Lawton Just what this viscosity is due to I would not wish to say Since the proteins are high polymers intermeshed and inter twined one would think of a molecular uncoiling process associated with the vibration The molecules moving against each other might produce the viscous behavior of this specimen

Alexander Problems of energetics have been touched on They may seem a little far afield and abstract but I think that some day we shall have to reckon squarely with them as illustrated by a report that came out of Georgia a few years ago Remington and Hamilton (76) calculated that under certain conditions as much as 40 per cent of the work done by the heart might be dissipated as the pulse wave traverses the aorta If that were applied to the clinical picture of a cardiac patient who may be wasting part of the energy expenditure of his myocardium because of the physical characteristics of blood vessels this may represent a very real prac tical problem

Burton Dr Lawton I think I should interject that you were using the word "viscosity" in the generalized physical sense that any force which depends upon the velocity of movement is called a viscous force it really has nothing to do with the restricted use of fluid viscosity and the coefficient of viscosity

A warning we should take is that Fenn (77) in analyzing the effects in striated muscle and the forces depending on the velocity of contraction showed that this coefficient which he called the viscosity has actually to do with the heat of shortening and nothing whatever to do with viscous forces in the other sense We should display the same caution here in interpreting it. You simply mean that this is a force proportional to the rate of change is that right?

Lawton I agree I should like to point out that the work of Peterson (17) seems to correlate with this type of curve He investigated, as was mentioned previously, the height of the acceleration transients, which plotted against the diastolic pressure also gave rise to a U-shaped curve with a minimum point in the region of 120 mm Hg. This was in the circulation of the intact dog

Heymans Did you observe any relationship between the condition of the arterial wall and hypertension?

Richardson What was the blood pressure of this 70-year-old man?

Lawton: I am afraid we do not have that particular pressure

Figure 60 is theoretically what might happen to various polymer

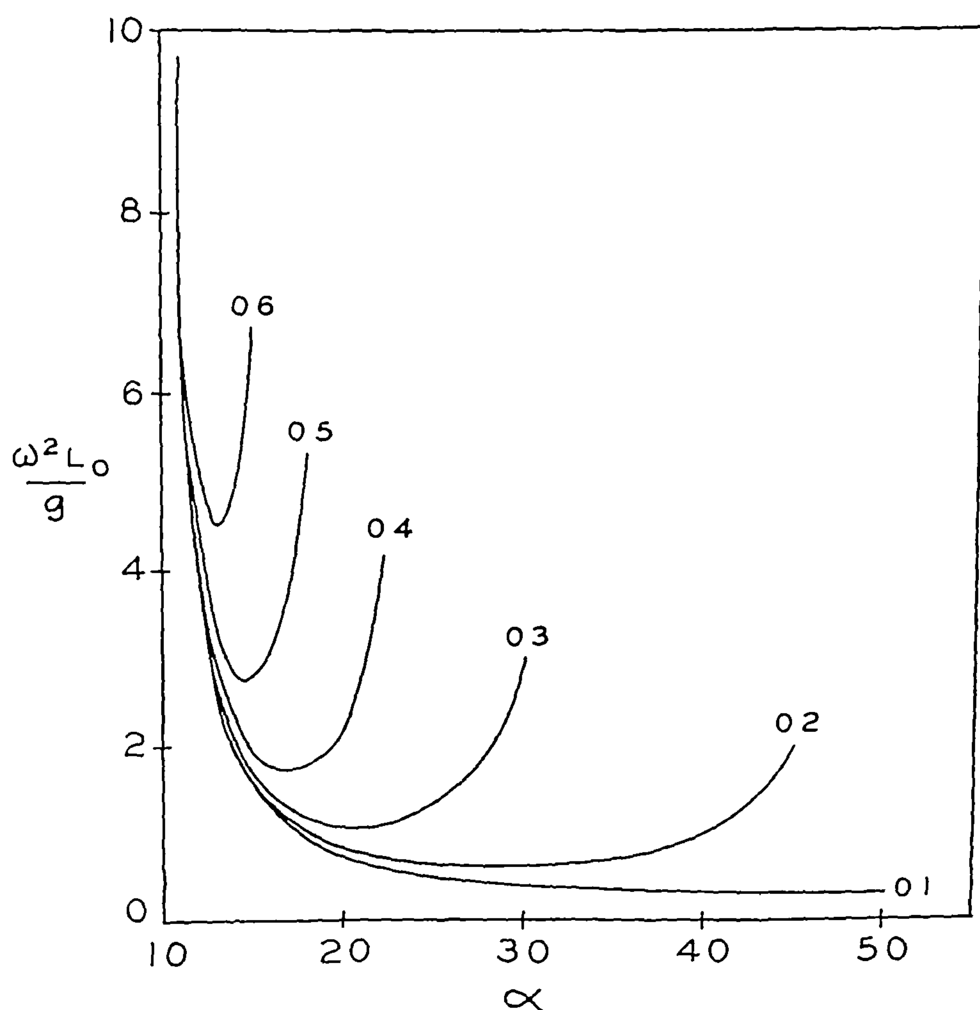


FIGURE 60 Theoretical frequency response curves of an ideal rubberlike material Values for the parameter of the equation from 0.1 to 0.6 are shown Reprinted, by permission, from Lawton, R W, and King, A L Free longitudinal vibrations of rubber and tissue strips *J Appl Physics* 11, *1310 (1951)*

systems subjected to the same sort of experiment This indicates the way the curve might move under increasingly stiffer conditions It is a theoretical calculation In actual point of fact latex rubber would be down somewhere between 0 1 and 0.2 the aorta would be up around 0 5 This will give you the general place of the aorta in the scheme of things

Kinsely The contour of the aorta is visible in the fluoroscope and it would be possible to measure the pressure by some modification of the contour technique Observations could be made on living men and the aorta could be removed at autopsy for histological examination

Lawton I am not so sure that it could be done so simply The best approach that I see to this problem is the one of Peterson of injecting a solution of saline into the aorta at various points and measuring the response of the system at each point This has not been followed up by studies of isolated aortic strips from the region

PARTIAL SUMMARY

Alexander Since the hour is getting on we might attempt to draw things together a bit This conference started with a discussion led by Dr Howard, which demonstrated that we are all still interested in the shock problem This was followed by an intensive discussion of some of the more recently described reflexes which we assume may supplement the better known buffer reflexes in maintaining circulatory homeostasis

Finally two other aspects have been brought out one is the distensibility characteristics of the peripheral vascular bed particularly on the venous side which determine the distribution of the blood volume The other problem is the evidence which has been presented of autonomous or local regulation of peripheral resistance in a decentralized vascular bed

An important field which we must explore in the future is I believe the manner in which the reflexes influence the peripheral mechanisms As one preliminary suggestion may I illustrate this with the experiment shown in Figure 61

The curves show the rise in venous pressure in the hind leg accompanying injection of blood into the femoral artery as we have described earlier In this case the dog was under chloralose and the sciatic and femoral nerves were intact The animal was vagotomized and a carotid sinus isolated and connected with a pressure bottle so that an essentially physiological stimulus could be delivered to the presso-receptor In the upper curve pressure in the isolated sinus was zero Blood pressure in the animal was at the

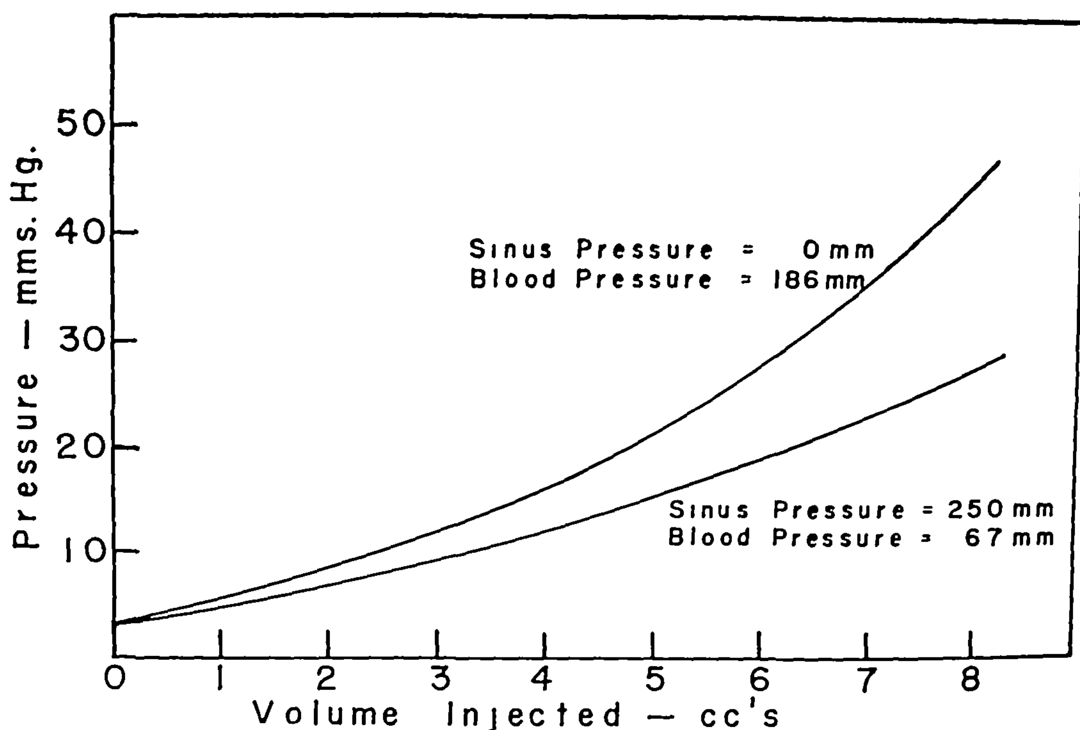


FIGURE 61 Influence of carotid sinus stimulation on the venous pressure rise in an innervated hind leg preparation As outlined in the text, the start of the venous pressure rise was interpreted as the start of the volume increment in the venous system, in this figure, as in other figures, volume units on the abscissa are equivalent to time units on the original recording

hypertensive level of 186 mm Hg since, of course, one observes a neurogenic hypertension under these circumstances

The pressure in the carotid sinus was then raised to 250 mm This produced a depressor response in the animal, with a fall in blood pressure to 67 mm Injection of blood into the hind leg under these circumstances yielded the lower venous pressure curve in Figure 61 The difference in the distensibility curves observed under these two conditions was quite reproducible

As is evident from our earlier discussion, a great many questions have to be answered before we will be ready to make a quantitative interpretation of the meaning of these venous curves recorded from the hind leg However, I think it is interesting that we are getting a response, which, I think, is dominantly on the venous side I offer this as just one suggestion of the type of work which I think should lie ahead of us

Heymans In your opinion, are the presso-receptors stimulated at the zero pressure level in the isolated carotid sinus preparation?

Alexander Your opinion is worth much more than mine It is

my assumption that I am removing stimulation Am I wrong in that assumption?

Heymans Our experimental observations (78) showed that a pressure of about 50 mm Hg in the carotid sinus induces no stimulation of the presso receptors If the pressure in the carotid sinus is decreased from 50 to 0 mm Hg the presso-receptors are however stimulated and the systemic blood pressure falls just as if the intra carotid sinus pressure would have been raised from 50 to 90 mm Hg As the presso-receptors are stimulated by the tension of the arterial wall we believe that the minimum tension of the arterial wall of the carotid sinus is situated at an intracarotid sinus pressure of about 50 mm Hg

Comroe However Dr Alexanders animal *did* react with hypertension at that time

Heymans If the intracarotid sinus pressure is decreased from 50 to 0 mm Hg the arterial wall of the carotid sinus bends to the inside of the lumen of the artery This bending of the arterial wall increases the tension of the wall and provokes a stimulation of the presso-receptors just as though the arterial wall had been bent in the other direction by an increase of the intracarotid sinus pressure above the 50 mm Hg level Thus in our opinion a zero pressure in the carotid sinus does not remove the stimulation of the presso-receptors The stimulation is removed when the pressure in the carotid sinus is about 50 mm Hg The relationship between the pressure in the carotid sinus and the systemic blood pressure thus is not linear

Liljestrand Is that due to stimulation of chemoreceptors?

Heymans No to pressure The chemoreceptors are out

Liljestrand But not in Dr Alexanders experiment?

Alexander Yes

Heymans It is a closed pocket

Alexander That is a very interesting point that I think we should consider However I trust you agree with me that at 200 mm. pressure there is much more stimulation than at 0 mm. pressure

Heymans I agree But I wish to point out that according to the observations of Koch and of ourselves the greatest sensitivity to pressure variations of the carotid sinus presso-receptors in dogs is situated at an intracarotid sinus pressure corresponding to the level of the normal arterial pressure of about 120 mm Hg The rate of fall of the systemic arterial pressure diminishes progressively when the intracarotid sinus pressure is raised progressively from 120 to 235 mm. Hg The lowest level of the systemic arterial pressure

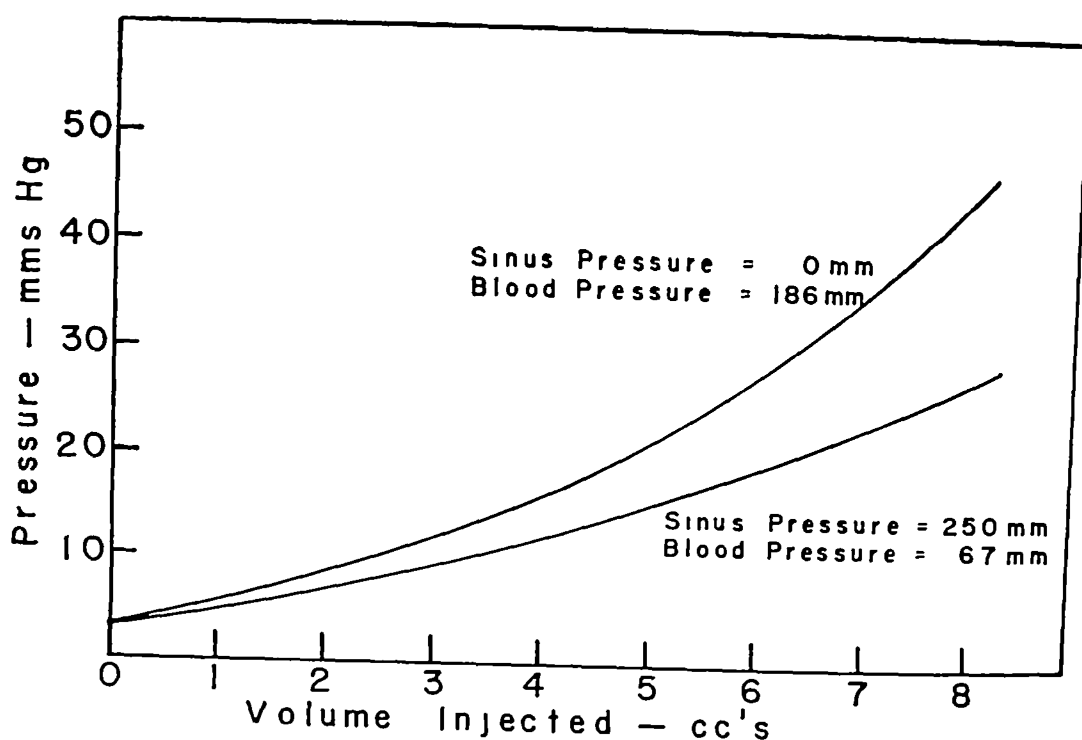


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occurs at the moment that the intracarotid sinus pressure has been raised to 235 mm Hg The curves of the intracarotid sinus pressures, and of the systemic arterial pressures are, however, not linear

Knisely Professor Liljestrand, we spoke earlier about blood flow through local regions of the body or specific organs Professor T Sjostrand (79,80), from your laboratory, has published experiments on lung as a blood depot I have tried to keep up partially with findings on the lung as a reservoir, but I should be most grateful if you would care to remark on work that has been done since then, either in your laboratory or elsewhere

Liljestrand I am not prepared to give a review of this subject, but I know that Sjostrand has continued to work on it a great deal and is still of the opinion that he is right Of course, that has been challenged from other quarters However, that there is an accumulation of blood in the lungs under certain conditions is undoubtedly true, but whether it can be said that the lungs serve as a reservoir for blood is, of course, a question of definition I think that the observations mentioned can be confirmed Interpretation is always somewhat subjective, and on that point there are still differences

Knisely When you were speaking, I could not help but think of the fact that there has been talk of the shifting of blood from one part of the body to another The reactions you were talking about certainly did so

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